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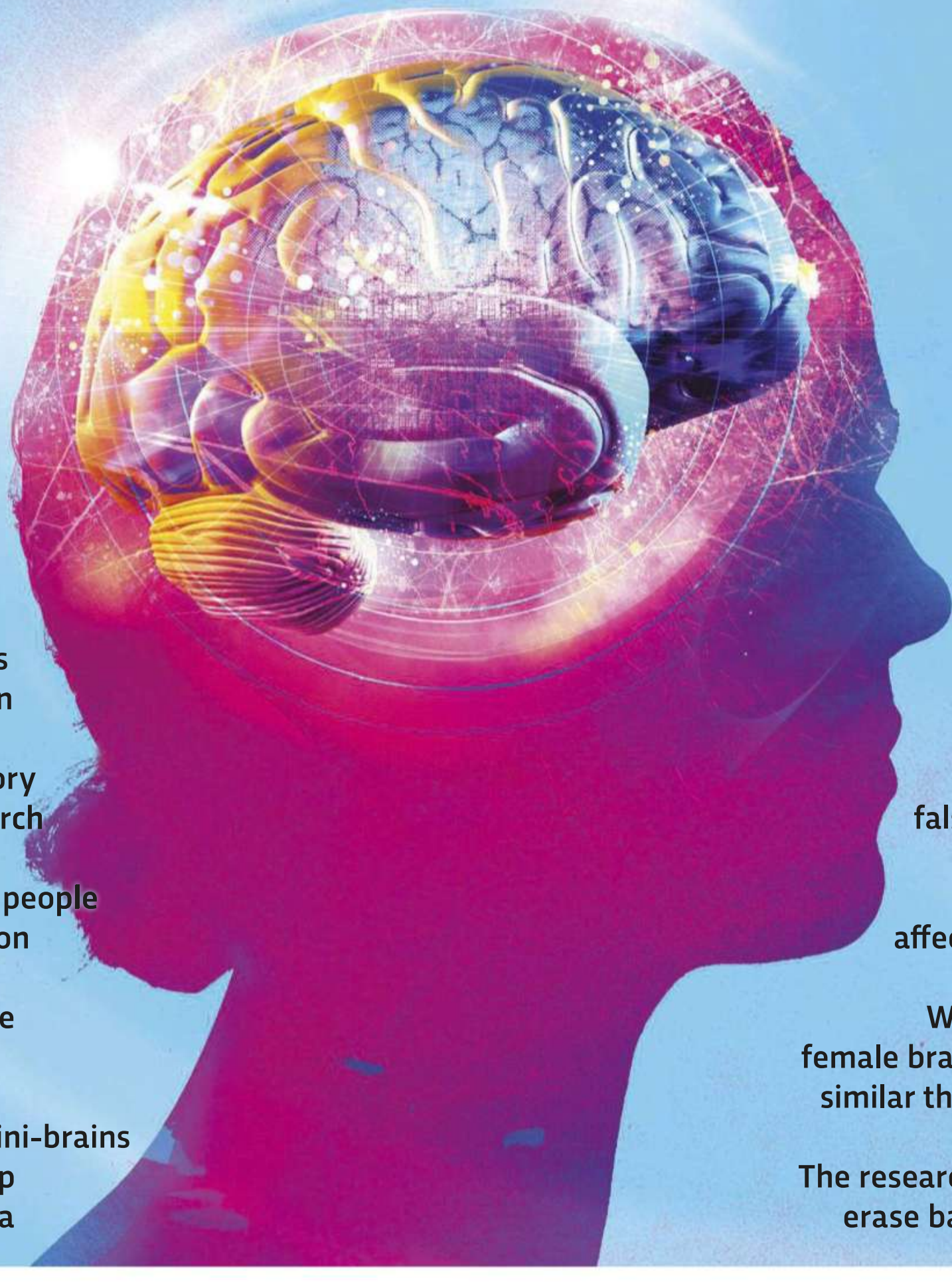
Science Focus
MAGAZINE
COLLECTION

THE BRAIN EXPLAINED

Decoding the secrets of your grey matter



How emotions fool your brain

The gory history of brain research

New hope for people with depression

How we define mental illness

Lab-grown mini-brains that could help treat dementia

What makes you *you*?

Why we get false memories

How stress affects your DNA

Why male and female brains are more similar than you think

The research that could erase bad memories

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Welcome

Inside each of our skulls is an organ weighing about 1.3 kilograms. The brain might look like an unimpressive lump of grey matter, but appearances can be deceiving. Its inner workings are so complicated that scientists still do not fully understand how it operates, and it's prone to diseases like dementia and Parkinson's that we are able to control and manage, but still cannot cure.

In this special edition, we try and find out everything we can about the brain. We investigate why and how scientists first started getting interested in brain research in the first place, and take a look at the (somewhat gory) early experiments that helped them find out more (p6). We also delve into the anatomy of the brain (p12) and discover what makes you *you* (p20). Speaking of which, you know the old adage that 'men are from Mars and women are from Venus'? Well, it turns out that our brains are actually pretty similar... (p46)

Elsewhere, we meet the scientists who are growing 'mini-brains' in the laboratory, in order to understand more about brain development and diseases like Alzheimer's (p60). We also investigate the causes of depression and some of the treatment options that could be on the horizon (p80).

And if endless cups of coffee just aren't cutting it on a Monday morning, take a look to see whether brain stimulation devices could help you unlock the true awesomeness of your mind (p86).

Enjoy the issue!

Alice Lipscombe-Southwell, Editor

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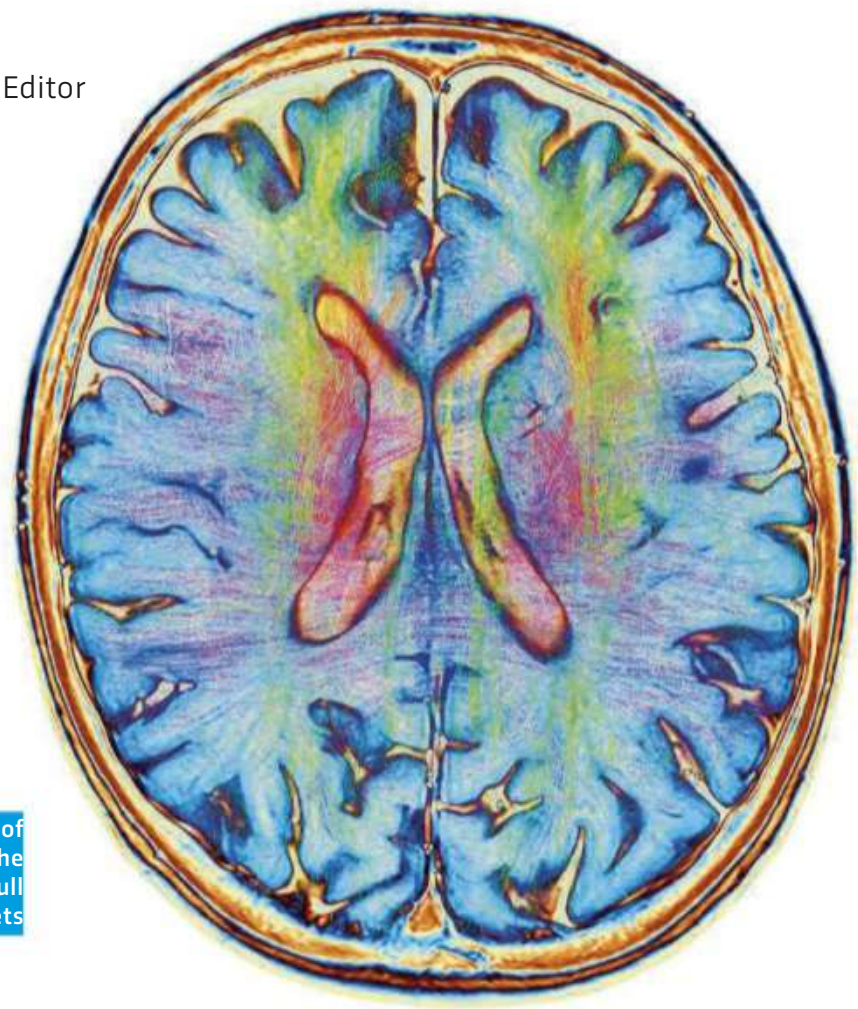

↗ Despite decades of brain research, the organ inside your skull still holds many secrets

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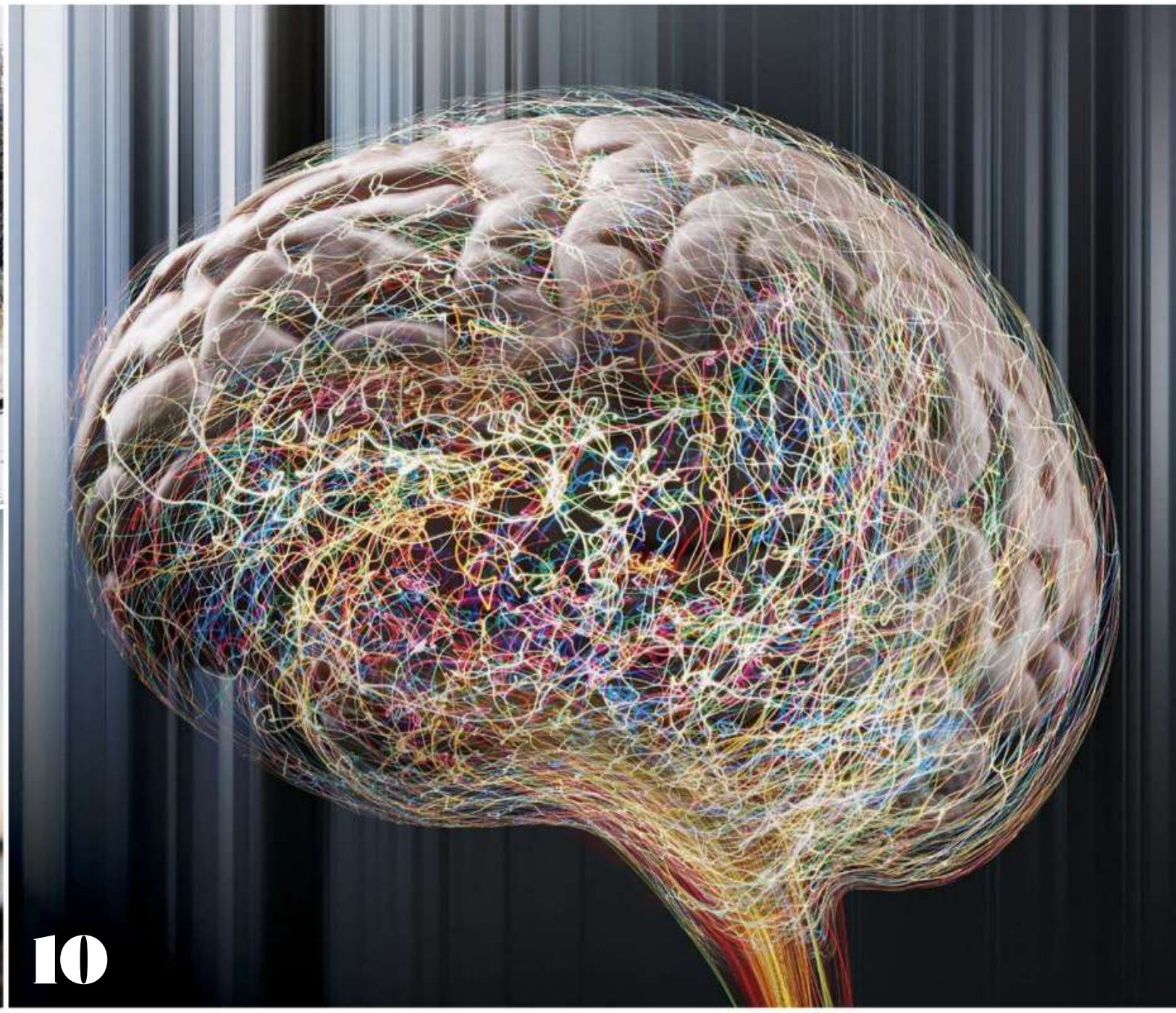
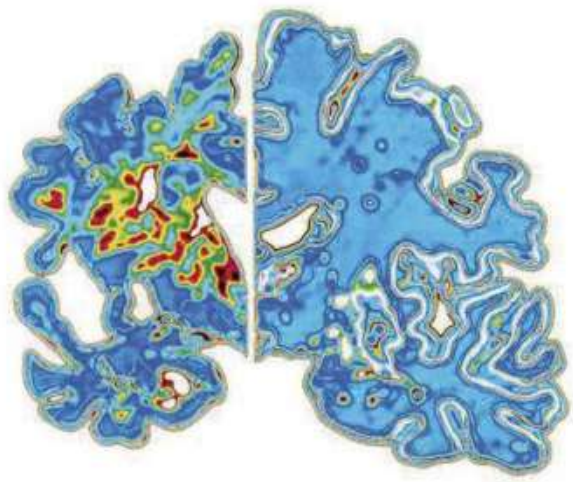




THE HISTORY OF BRAIN RESEARCH

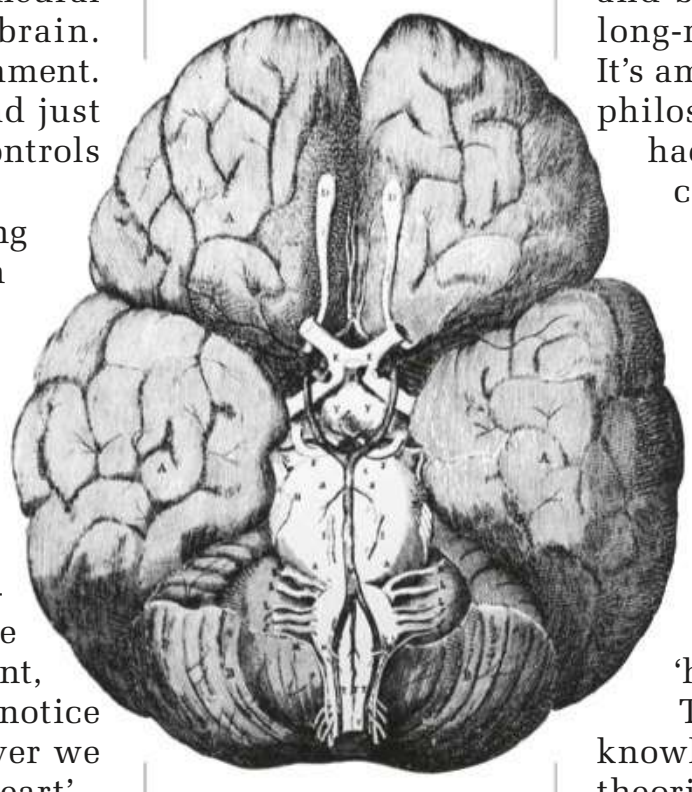
Doctors and neuroscientists have been attempting to unravel the secrets of the brain for centuries – but it has proved a tough nut to crack. We look back at the major discoveries

by CHRISTIAN JARRETT

Rome, 2nd Century AD. An audience of philosophers and politicians have gathered to watch Galen of Pergamon, the 'prince of medicine', perform a public demonstration involving a pig. The animal's squealing falls suddenly silent as Galen severs its laryngeal nerve – the neural link connecting its voice box to its brain. The crowd audibly gasps with astonishment. Why were they so shocked? Galen had just proved that the brain, not the heart, controls behaviour.

This might not sound groundbreaking to our modern ears, but the historian Charles Gross describes it as "one of the most famous single physiological demonstrations of all time". Although Galen wasn't the first to recognise the functional importance of the brain, he was the first to carry out a public experiment supporting his case. In Galen's time, the 'cardiocentric view' – the idea that thought, mind and soul are located in the heart – remained dominant, and would do so for centuries. You'll notice that its legacy lives on today, whenever we use sayings such as 'learn things by heart'.

The pig demonstration reflects the longer story of how we've come to understand the brain – it's a tale of colourful characters, ghoulish experiments, and stubborn myths.



Christopher Wren's highly detailed illustrations complemented Thomas Willis's writings about the brain's anatomy

CURDS AND SPIRITS

Throughout much of history, our understanding of the brain was often more of a philosophical than a scientific pursuit. This is partly because, until the last century, the biological study of our grey matter was mostly dependent on post-mortem investigations of animal brains and bodies, and more rarely – thanks to a long-running church ban – human brains. It's amazing to think that as late as 1652, the philosopher Henry More wrote that the brain had no more capacity for thought than "a cake of suet or a bowl of curds".

One of the most influential brain dissectors who helped overturn these beliefs was the English doctor Thomas Willis. He authored the magisterial book *The Anatomy Of The Brain*, published in 1664. Willis made astute and visionary arguments that complex mental functions are carried out by the cerebral cortex. This part of the brain had long been seen as little more than a useless 'rind' – cortex means 'rind' or 'husk' in Latin.

The continuing lack of scientific knowledge about the brain allowed mistaken theories to survive until relatively recently – theories that seem absurd by modern standards. For example, another long-running belief (this one strongly endorsed by Galen) was that the brain pumps 'animal spirits' around the body.

LIGHT SHOW
Even as late as the 17th Century, some people thought the brain was a flabby organ, incapable of thought. But as this artist's impression shows, the organ is filled with a stunning array of nerve cells (neurons), each playing a vital part in helping the brain to regulate and control the mind and body ↙

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Our leading physicians and scientists believed right up until the 18th Century that nerves were filled with these animal spirits – bizarre entities that the philosopher René Descartes described as "a very fine wind". The breakthrough that led to this idea being overturned had to do with electricity, and specifically the emergence of 'electrotherapy' as a treatment for paralysis.

Public demonstrations again played their part in changing minds. In an event held in 1803 in London, for example, Giovanni Aldini (nephew of the pioneering anatomist Luigi Galvani) applied electricity to George Forster's brain to show how it caused the muscles of his face to twitch. Forster didn't know much about this – he'd just been hanged for the murder of his wife and child. But for the audience, it helped to show how electricity was part of the way that nerves communicate.

However, even as the scientific establishment came to recognise the functional significance of the brain, and especially the cerebral cortex, another mistaken dogma persisted – the idea that mental functions, such as language, are distributed uniformly throughout the cortex rather than being partly localised in specific regions.

"In 1803, Giovanni Aldini applied electricity to George Forster's brain to show how it caused the muscles of his face to twitch"

One historical patient played a particularly important role in helping to overturn this idea. His name was Louis Victor Leborgne, but he was nicknamed 'Tan' because this was virtually the only word he could utter. At autopsy, the French neurologist Paul Broca discovered that Leborgne had highly localised damage to a region in his left frontal cortex, known today as Broca's area, and he inferred that the damaged region must play an important role in speech. Broca's presentation of Leborgne's case to the Société d'Anthropologie and the Société ➤

“Previously, researchers had to make assumptions, but with EEG they could see how different brain regions became more active”

Anatomique in 1861 was instrumental in convincing the academic community that language function is largely dependent on the frontal lobes. The historian Stanley Finger describes this as a “turning point in the history of the brain sciences”. Patients like Leborgne, with particular mental or physical deficits tied to specific areas of brain damage, have been one of the most important sources of information about the brain, and this is still true today.

At the end of the 19th Century, brain science was focused once again on the perplexing issue of how exactly nerves communicate with each other. While the earlier realisation of electricity’s role had helped to debunk the notion of animal spirits, it was clear that there was more to nerve communication.

NERVOUS SCIENCE

We now know that electrical current along a nerve cell (neuron) causes it to release chemicals across a tiny gap – a synapse – and these chemicals (neurotransmitters) are then picked up on the other side by the receiving neuron. But in the late 1800s, even the best microscopes were incapable of revealing these gaps between neurons. This led the Italian scientist Camillo Golgi and his colleagues to propose that nerves are fused together – an erroneous idea known as the ‘reticular theory’ (from the Latin for ‘net’).

It was the Spanish neuroscientist Santiago Ramón y Cajal who killed off the nerve net idea thanks to his advances in cell staining techniques, which made it clear that neurons are not joined together after all.

In the 20th Century, technology began to play an increasingly important role in advancing our knowledge of the brain, particularly by allowing psychologists and neuroscientists to monitor brain activity. In the 1920s, scientists started to use electroencephalography (EEG), which involves recording electricity emitted by the brain through electrodes placed on the scalp. Previously, researchers had to make assumptions about the location of different mental functions based on the effects of brain injury and by looking for patterns of damage at post-mortem. With EEG they could see how different regions of the brain become more active depending on what the person was saying, thinking or doing. But the problem with EEG is that while it provides good temporal resolution – revealing changes in brain activity from one millisecond to the next – its spatial resolution is crude. This limitation was overcome in the 1960s with the advent of

TIMELINE: BRAIN SCIENCE

425 BC

The Hippocratic treatise *On The Sacred Disease* states, contrary to the dominant cardiocentric view, that “from the brain and the brain only arise our pleasures, joys, laughter, and jests, as well as our sorrows, pains, griefs, and tears.”

GALEN OF PERGAMON (c.130-210)

In the 2nd Century, the philosopher performs the pig demonstration, showing that the brain controls behaviour.

1543

Renaissance anatomist Andreas Vesalius publishes his landmark book *On The Fabric Of The Human Body*, showing some of the most detailed dissections of the human brain ever produced.

1830s

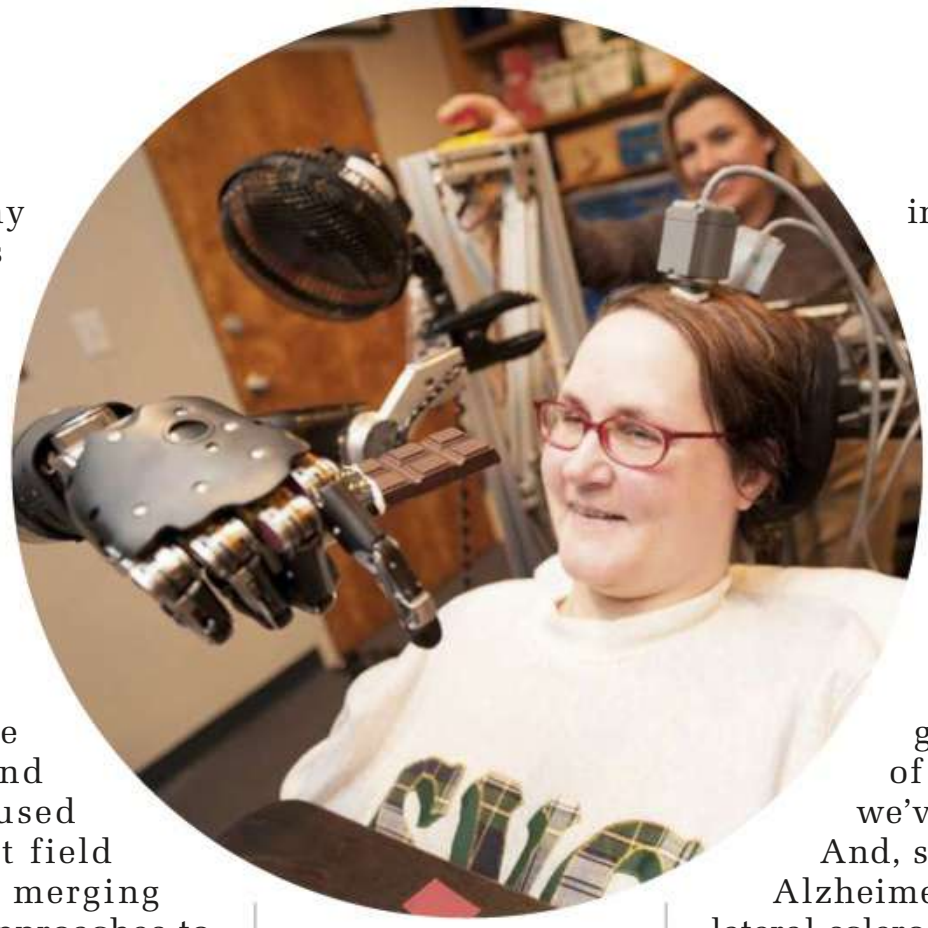
Phrenology reaches the peak of its popularity. This was the mistaken idea that psychological aptitudes and personality traits can be discerned from the bumps on someone’s skull.

1848

Railway worker Phineas Gage becomes one of the most famous patients in neuroscience after surviving an accident in which an iron rod passes straight through the front of his brain.

positron emission tomography (PET), which allowed researchers to monitor changing patterns of blood flow in the brain in high resolution. Things progressed even further in the 1990s with the emergence of functional magnetic resonance imaging (fMRI), which also has good spatial resolution but, unlike PET, does not require the injection of a radioactive isotope.

fMRI has had a huge influence on the study of the brain, and is now the main technique used in the increasingly dominant field of cognitive neuroscience, merging psychological and biological approaches to brain function. These are the kinds of studies that lead to colourful images of 'blobs on the brain', where the blobs usually illustrate areas thought to contain heightened activity as the participant performs different tasks. In 2013, a review of the field estimated that over 130,000 fMRI research studies had been published, a figure that will by now be substantially higher.



Quadriplegic Jan Scheuermann uses thought to control a robotic arm

NEXT STEPS

Increasingly sophisticated methods for recording and decoding brain activity have helped contribute to important neuroscience breakthroughs in recent years. For example, there has been huge progress in brain-machine interfaces, which enable paralysed people to control computer cursors or prosthetic limbs using thought alone.

Other research has shown that it's possible to use recorded brain activity patterns to communicate with some patients who were previously thought to be in a non-communicative, persistent vegetative state.

But, although we've made great strides in our understanding of the brain, the truth is that we've barely scratched the surface. And, sadly, devastating illnesses like Alzheimer's (see p74) and amyotrophic lateral sclerosis still remain incurable.

Let's hope this changes with the record levels of investment being ploughed into ambitious new neuroscience research programmes, such as the BRAIN Initiative in the US and the Human Brain Project in Europe (see p92). A key player in the latter project is neuroscientist and entrepreneur Prof Henry Markram, who in a TED talk said: "It is not impossible to build a human brain." He said that in 2009 and in the 10 years since, his project has got a lot closer to reaching that goal. **SF**

by **DR CHRISTIAN JARRETT**

Christian is a neuroscientist and author of Great Myths Of The Brain *(£15.99, Wiley-Blackwell).*

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ALOIS ALZHEIMER (1864-1915)

In 1901, the German psychiatrist makes detailed notes on Auguste Deter, the first person diagnosed with Alzheimer's disease. "I have lost myself," she tells him.

SANTIAGO RAMÓN Y CAJAL (1852-1934)

In 1913, the Spanish neuroscientist publishes *Degeneration And Regeneration Of The Nervous System*, detailing his findings on brain injury and recovery. But he also claimed in error that new neurons do not grow in adult brains.

1953

Patient Henry Molaison undergoes brain surgery for intractable epilepsy. The procedure leaves him with profound amnesia and he becomes one of neuroscience's most studied individuals.

OLIVER SACKS (1933-2015)

In 1985, British neurologist Oliver Sacks publishes his bestselling book *The Man Who Mistook His Wife For A Hat*. He becomes renowned for chronicling the human stories of brain illness and injury.

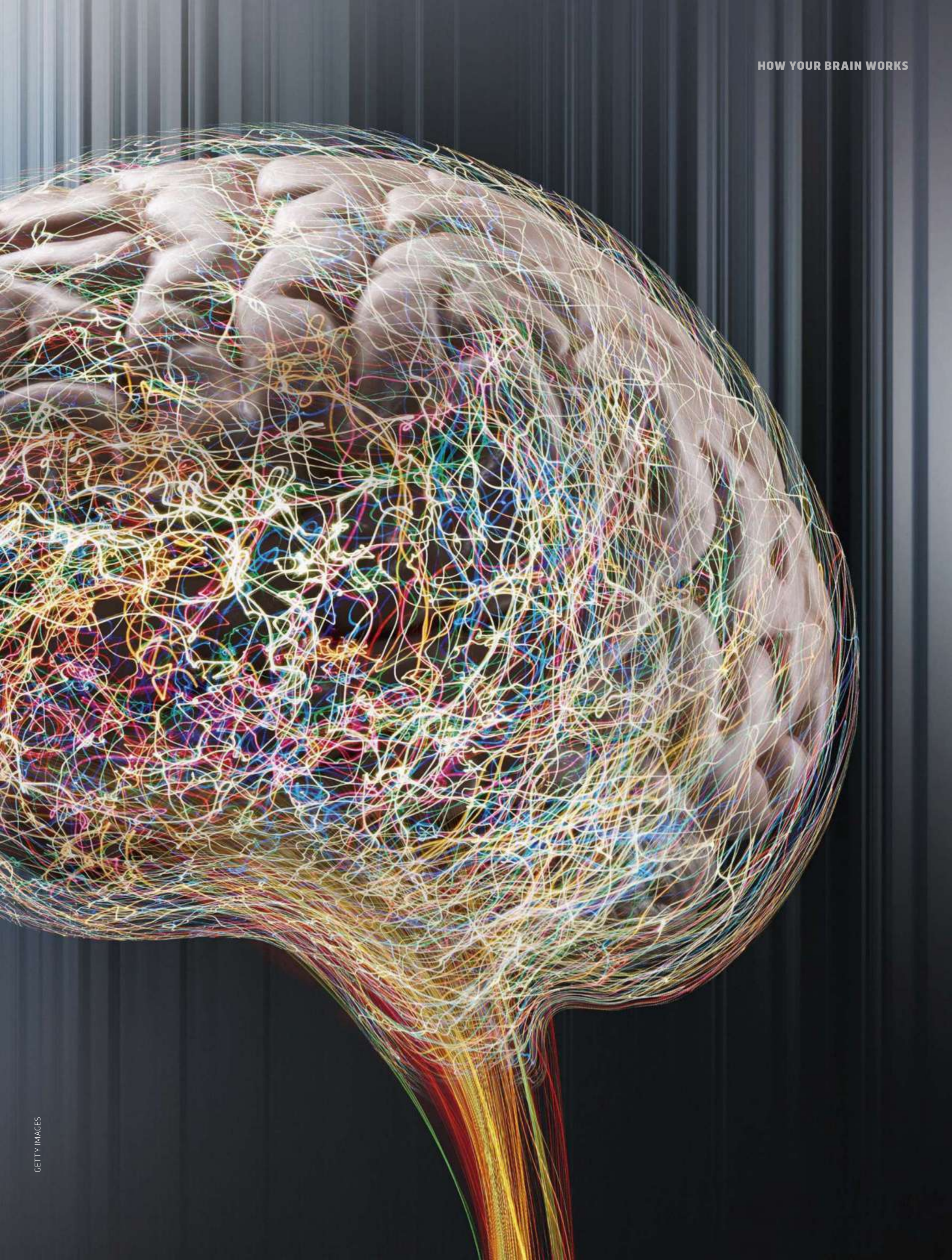
2013

President Barack Obama launches the BRAIN Initiative. "As humans, we can identify galaxies light-years away, we can study particles smaller than an atom. But we still haven't unlocked the mystery of the three pounds of matter that sits between our ears."

HOW YOUR BRAIN WORKS

Some say we know more about the ocean depths and distant cosmos than we do about the inner workings of our minds. Here's what we currently *do* know about the brain

by RITA CARTER



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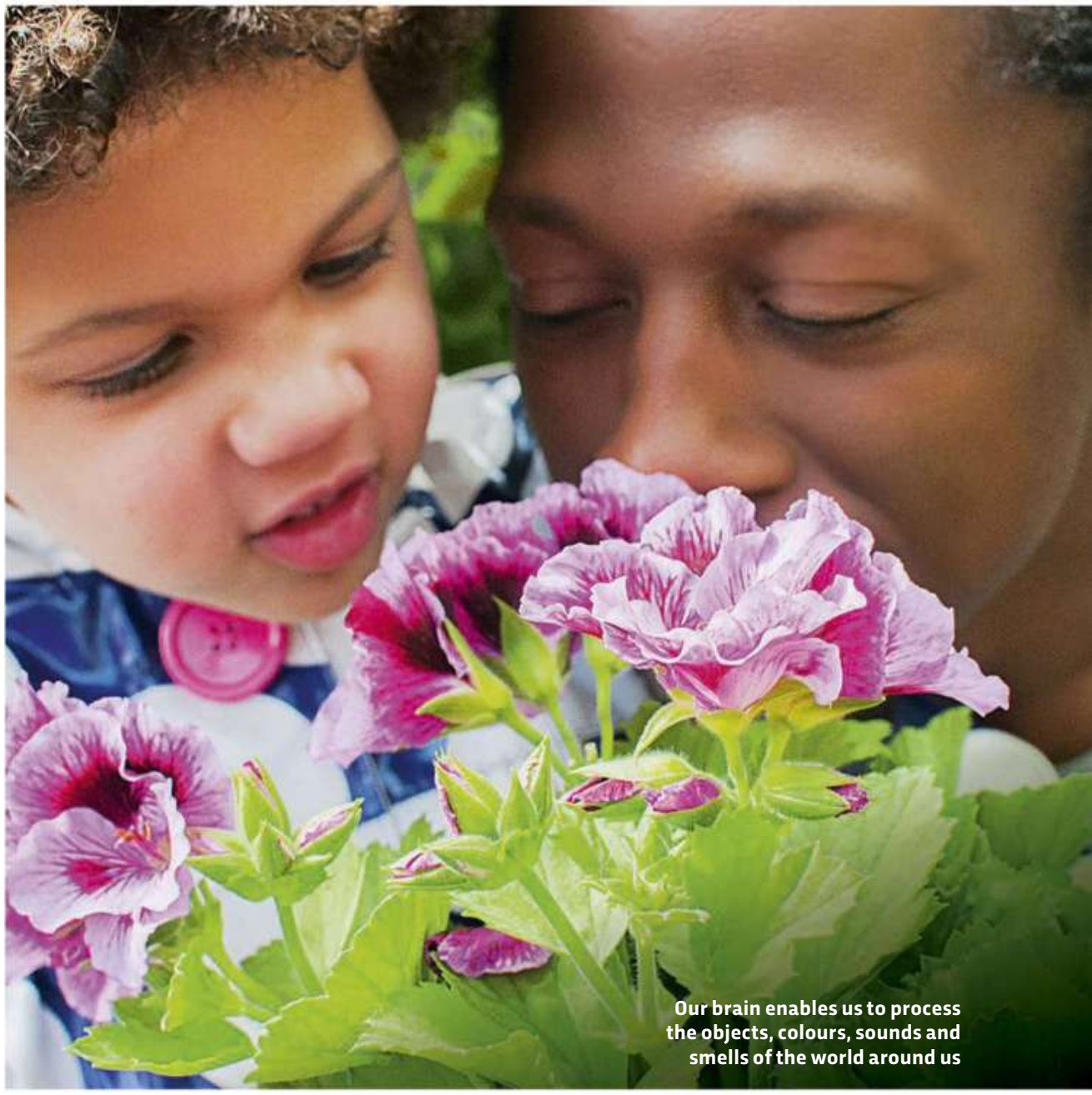

Our brain enables us to process the objects, colours, sounds and smells of the world around us

The brain is an electrical device that generates every one of our sensations, thoughts, feelings, and actions. Incredibly, it does all this on slightly less power than that used by a 60W lightbulb. Its primary purpose is to keep us alive by orchestrating and regulating our responses to the outside world. Most brain functions, such as adjusting heartbeat and triggering the release of hormones, occur without us knowing. Some brain function, however, has a special quality – consciousness.

Conscious awareness feels effortless, but the mechanisms underlying it are immensely complicated. The brain doesn't just make us aware of our surroundings – it constructs them.

The world seems to consist of objects, colours, sounds and smells. All that's really there, though, are light rays and sound waves, jittering atoms and vibrating molecules, all of which continuously bombard our bodies. The brain transforms these stimuli into familiar perceptions through a complex and surprisingly lengthy process. Up to half a second elapses, for instance, between light arriving at the eye and the emergence of a conscious image. If something goes wrong during that pre-conscious half-second, the result can be very strange. A person may see or hear things that are not there or fail to recognise what is. They might mistake familiar friends for strangers, or be unable to identify common objects.

One way to look at conscious processing is to think of the brain as a factory assembling elements of consciousness – known as 'qualia' – from the raw material of various types of stimuli.

"The brain's primary purpose is to keep us alive by regulating and orchestrating our responses to the outside world"

It starts when a stimulus hits a sense organ, such as the eye or ear. The organ reacts by generating an electrical signal that it directs along neuronal pathways – fibres made from linked electrical cells – to specialised brain areas. Retinal cells react to light, for example, sending a current of electricity down neural pathways to the occipital lobe at the back. Cells in the ear turn pressure waves into currents, which travel to the auditory cortex in the temporal lobe. And receptors in the nose react to certain molecules, triggering activity in a deep part of the frontal lobe. Long, snaking nerves that run down the spinal cord to the skin and muscles react to touch and pressure, sending signals back to the somatosensory cortex, a strip of tissue that curves around the top ➲

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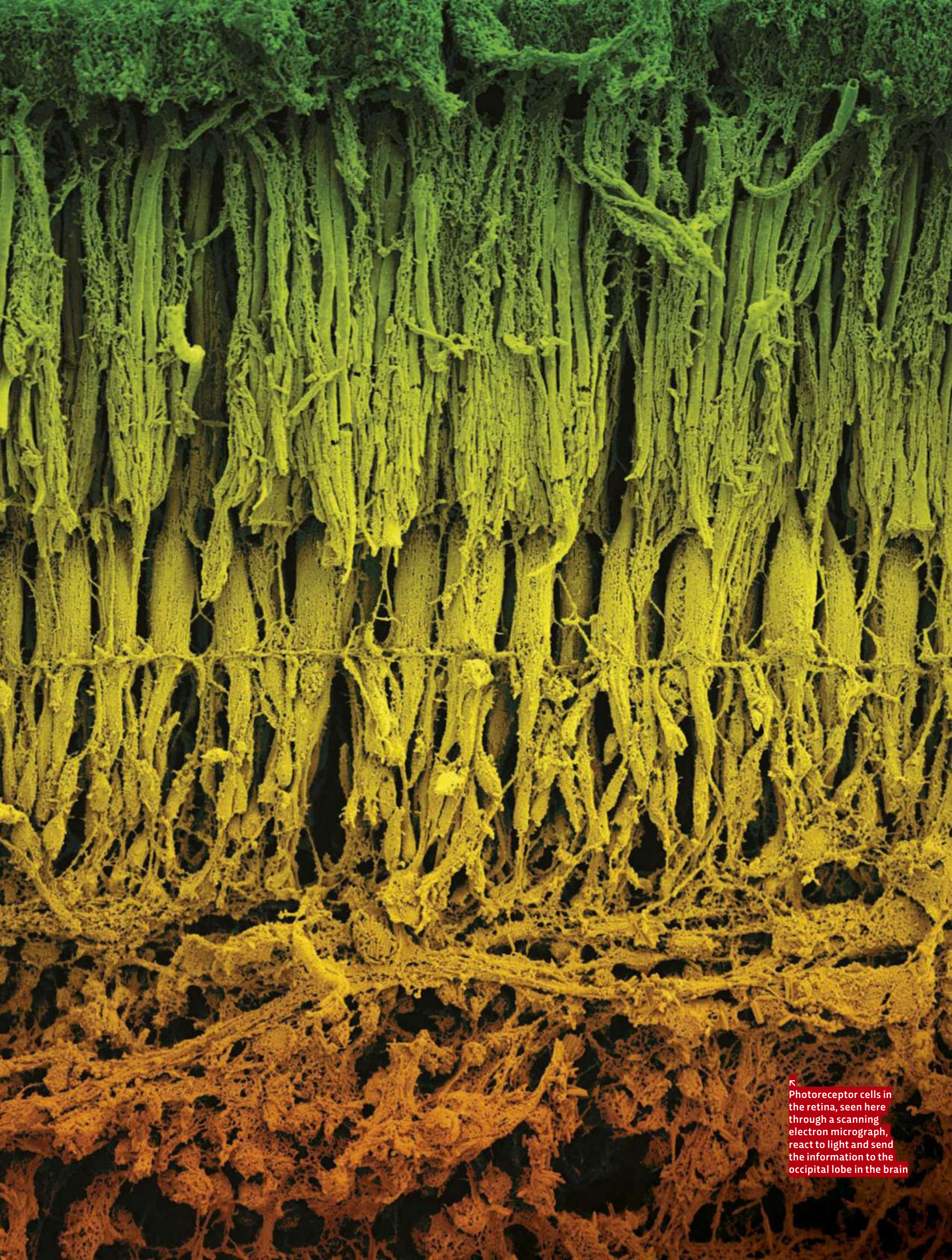


↖ Photoreceptor cells in the retina, seen here through a scanning electron micrograph, react to light and send the information to the occipital lobe in the brain

of the brain, like a headband. Once these signals reach the appropriate brain area, the business of transformation begins.

The construction of a conscious visual image starts when the light-generated electrical impulses travel back from the eye along neural pathways called the optic nerves. About halfway through the brain, the signals pass through the thalamus. This part of the brain acts like a relay station, receiving most incoming information and shunting it on to the right areas. It pushes the majority of visual information to the occipital lobe at the back of the brain, but it diverts some of it to the parietal cortex, close to the area concerned with action. This diversion creates an odd effect – we 'know' what our eyes have registered without actually seeing it.

BLINDSIGHT ROUTE

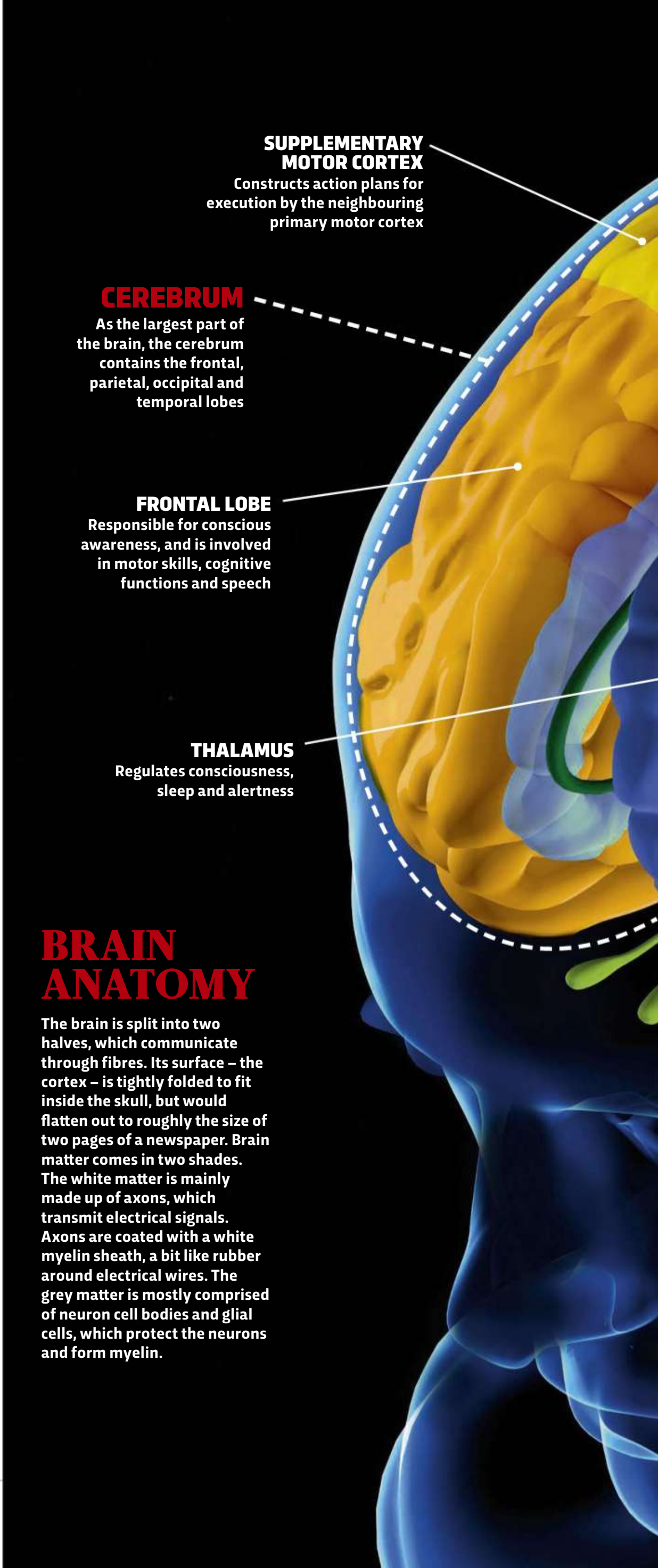
The phenomenon is known as 'blindsight' and it is observed most easily in people who are – in the ordinary sense – blind. Although they protest they cannot see, if forced to 'guess' where an object is by pointing at it, such people often get it right, to their astonishment. This is because the diverted signals activate parietal neurons, which orient us to targets. We don't consciously know what is there, but our brain does, and directs our body towards it.

Research on blindsight shows that it is not just an object's position in space that can be detected this way. One blindsighter can tell the shape, colour and trajectory of a target, and even read the expression on an 'invisible' face. Another can recognise faces even though he can't see them consciously at all.

Blindsight has also been demonstrated in people with normal vision. It probably accounts for things like the ability of elite tennis players to hit balls travelling too fast to be seen in the normal way.

Back on the main pathway, most signals from the eyes go to the occipital lobe at the back of the brain. This is made up of smaller areas, each of which specialises in one or another element of vision. The motion area, for example, discerns signals that encode movement, while another area responds to colours, and others to edges, depth, and so on.

The first stop for incoming visual information is the primary visual cortex, or V1 – a sort



BRAIN ANATOMY

The brain is split into two halves, which communicate through fibres. Its surface – the cortex – is tightly folded to fit inside the skull, but would flatten out to roughly the size of two pages of a newspaper. Brain matter comes in two shades. The white matter is mainly made up of axons, which transmit electrical signals. Axons are coated with a white myelin sheath, a bit like rubber around electrical wires. The grey matter is mostly comprised of neuron cell bodies and glial cells, which protect the neurons and form myelin.

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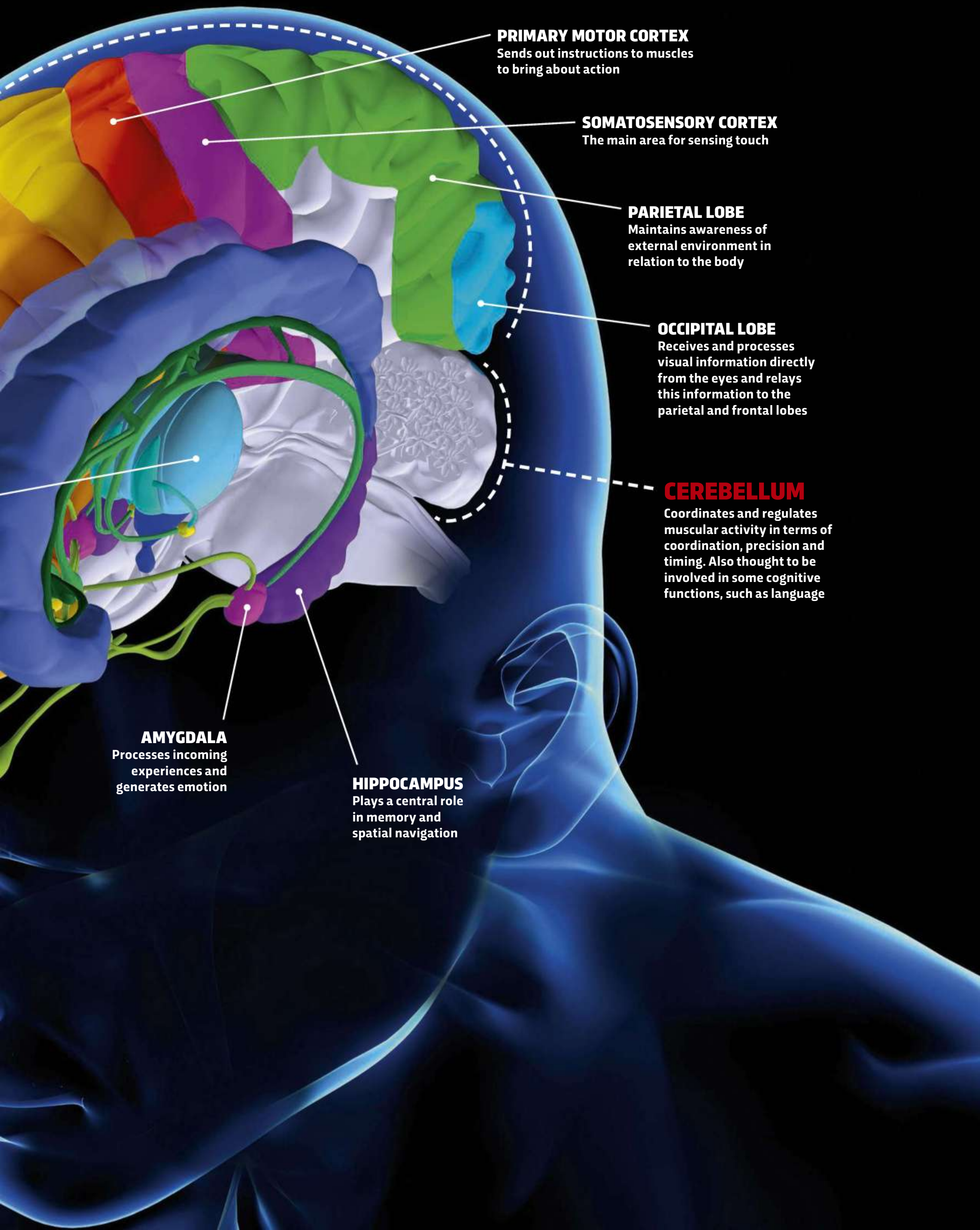
PRIMARY MOTOR CORTEX
Sends out instructions to muscles to bring about action
SOMATOSENSORY CORTEX
The main area for sensing touch
PARIETAL LOBE
Maintains awareness of external environment in relation to the body
OCCIPITAL LOBE
Receives and processes visual information directly from the eyes and relays this information to the parietal and frontal lobes
CEREBELLUM
Coordinates and regulates muscular activity in terms of coordination, precision and timing. Also thought to be involved in some cognitive functions, such as language
AMYGDALA
Processes incoming experiences and generates emotion
HIPPOCAMPUS
Plays a central role in memory and spatial navigation

of checking-in depot for visual information, which lies at the very back of the brain. V1 registers that something potentially visual has come in and then pushes the electrical signals back towards the front of the brain. It is a little bit like the factory conveyor belt has done a U-turn.

In quick succession, the information passes through the specialised visual areas, each of which detects and amplifies their relevant thing – such as colour or movement. This turns the signals from simply a visual stimulus to one endowed with qualities, such as red, spherical and moving; or square, black and static. As it travels through the occipital lobe, the information splits and continues its travels along several divergent pathways. One of the routes goes up and over the brain to the parietal cortex, while another ducks along the bottom edge of the temporal lobe.

THE 'WHAT?' PATHWAY

The lower route is known as the 'what?' pathway, because it goes through those parts of the brain that, bit by bit, build the information into a recognisable, and possibly conscious, image.

The temporal lobe is the part of the brain where long-term memories are encoded and retrieved. Memories reside in networks of interconnected neurons. To be precise, these are potential memories – the experience that formed them is only brought to mind if electricity sparks up in the network and sets the neurons in it firing. Such activation occurs when a novel event maps on to a memory by activating some of the same neurons as the previous experience. For instance, if an incoming signal has been 'tagged' by the visual colour area as red, and the shape area as round, it will trigger ignition in the 'red and round-detecting' neurons in memory networks formed by previous experiences of red, round things. Hence, the new information may bring to mind apples, red balls, and alarm buttons. The one that most closely matches the current information will then be attached to it, so the signal moves forward as 'apple', rather than just 'red and round'.

This (still unconscious) matching of new information to old is crucial for recognition and, if it fails, the result can be weird. A person may be able to see an object, describe it, draw it, and even use it – yet be unable to identify it. "A brush?" queried one such person, in response to a carrot. And (confidently) to a picture of a nose: "Ah – a soup ladle!"

'Agnosia', as it is called, varies widely according to which stage of temporal lobe processing is compromised. One section of the 'what?' pathway deals exclusively with distinguishing people. The late Oliver Sacks wrote of a college professor with damage to this area who "genially, Magoo-like… might pat the heads of water hydrants and parking meters, taking these to be the heads of children…[and] would amiably address carved knobs on the furniture and be astounded when they did not reply." More commonly, people know when they are looking at a person but cannot distinguish one face from another, a condition known as

The blindsight phenomenon is thought to be the reason elite tennis players are able to react to balls that appear to move too fast for the human eye to see

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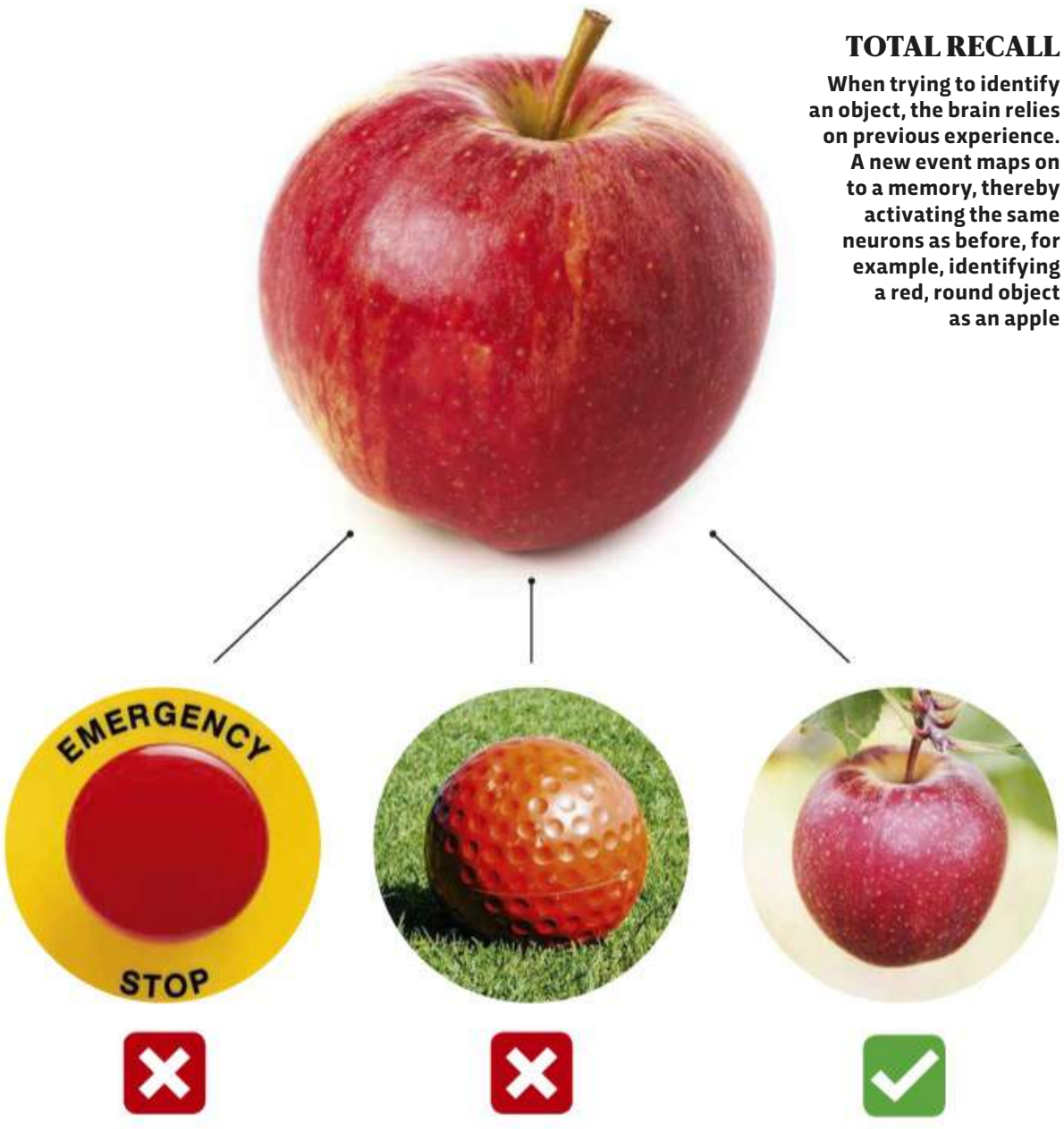
"Prosopagnosics may not even recognise their own partners – a situation fraught with potential disaster"



TOTAL RECALL

When trying to identify an object, the brain relies on previous experience. A new event maps on to a memory, thereby activating the same neurons as before, for example, identifying a red, round object as an apple

'prosopagnosia'. Prosopagnosics may not even recognise their own partners – a situation fraught with potential disaster.

THE INTRIGUING CASE OF HM

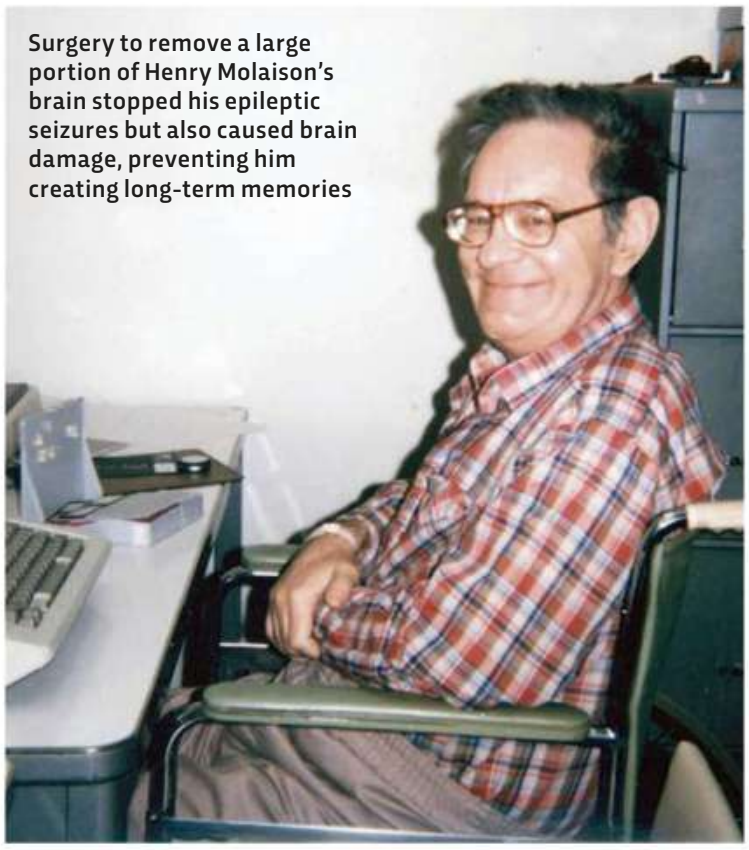
Further along the 'what?' pathway, visual signals are matched to personal rather than merely generic memories. An object tagged so far as a face, for instance, may now become 'Bob's face'.

This type of recognition happens as the signals pass the hippocampus, a tiny nugget of tissue that records and recalls personal experiences. Its central role in memory makes hippocampal damage potentially catastrophic.

The case that best demonstrates this is that of Henry Molaison, known to generations of psychology students as 'HM'. As a young man Molaison suffered severe epilepsy, and in 1953 doctors removed a large section of his brain to prevent the seizures from spreading uncontrollably. Unfortunately the area they removed included his hippocampi and, although the surgery succeeded in stopping his seizures, it completely robbed him of his ability to lay down any new memories. He experienced his long life, apparently fairly normally, from moment to moment, but the experiences did not stick. In his head he remained the young man he was before surgery and, however many times he met a person, he never remembered them. Indeed, if he was distracted for just a few seconds, his memory of what he was doing and who he was talking to evaporated.

One of the many researchers who introduced herself to Molaison repeatedly was Suzanne Corkin, professor of behavioural neuroscience and head of the Corkin Lab at the Massachusetts Institute of Technology before her death in May 2016. Corkin recalled that Molaison loved to relate his few clear memories of his childhood, over and over, and how the face he surprised himself with in the mirror each morning, did not quite connect with them.

"The interesting and important thing scientifically about these stories was that he would give you the gist of them, but they were never linked to a specific time and place," Corkin told *The Guardian* in 2013. "You and I can say what we did on our last birthday. But Henry could never remember what else happened. There were no connections, no



Surgery to remove a large portion of Henry Molaison's brain stopped his epileptic seizures but also caused brain damage, preventing him creating long-term memories

associations for him in that way."

Yet he retained some types of memory – he learned to play new tunes on the piano, for instance, but with no recollection of learning them. So, as well as illuminating the crucial function of the hippocampus, his case helped researchers to tease apart and locate the structures involved in different types of memory – long and short term, semantic and episodic – which allow us to navigate the world.

The hippocampus is one of the areas most affected in Alzheimer's dementia, but otherwise, the damage to it is mercifully rare – most memory lapses are simply due to inattention. Indeed, inattention prevents the vast majority of incoming information from becoming conscious. Only very strong signals – those which grab attention – continue from the temporal lobe to the end of the 'what?' pathway in the brain's frontal lobe.

The frontal lobe is the part of the brain responsible for conscious awareness. Thoughts, emotions and perceptions are constructed in unconscious areas further back, but if they get pushed forward to the frontal area we may become aware of them.

It's not necessary, though, for us to be conscious of something in order to act on it. Indeed, sometimes consciousness can be positively disadvantageous – think of what happens on a dance floor when we become conscious of what our feet are doing. Hence, our bodies may act on information long before it finishes that tortuous journey along the 'what?' route.

ABOVE The amygdala reacts to information it receives and generates an appropriate emotion

JENNI OGDEN / OXFORD UNIVERSITY PRESS, GETTY IMAGES X 2

THE 'WHERE?' PATHWAY

While some signals travel along the 'what?' pathway, other versions of the information shoot along faster routes. One is the upper or dorsal stream, which ends in the parietal cortex. This is known as the 'where?' pathway, because the areas it passes through are concerned with acting on the information, rather than working out what it is. The speed of the 'where?' pathway (part of which joins with the blindsight route) means that your body is primed and ready to act on new information before it becomes conscious.

Another fast track carries signals through the amygdala. This tiny nucleus 'tastes' all incoming experience and reacts to it by generating appropriate emotion. Emotions are primarily bodily reactions – the feelings we call 'sadness' or 'joy' are just our conscious knowledge of physical changes that have already occurred.

"Conscious emotion is, in a way, a red herring," says New York University's Prof Joseph LeDoux, who is an expert on the amygdala. "Emotions are things that happen to us,

The amygdala helps us to evaluate information as 'good' or 'bad', kicking us into action, such as running from a snake

rather than things we make happen. We try to manipulate our emotions, but all we are doing is arranging the outside world so it triggers certain emotions – we cannot control our emotions directly. Our feelings often push out thinking, whereas thinking fights a mainly losing battle with emotions."

Incoming information is 'tagged' as good or bad by the amygdala about a quarter of a second before we are conscious of it. And, as we have seen, the 'where?' pathway ensures that our bodies are primed to act on it in about the same time. So if the amygdala evaluates an event as 'bad' we may move away from it, or hit out at it before we know consciously that it is there. A snake in the grass can set us running away and, conversely, signals from a smiling face will start our own smile muscles twitching even if the face it decorates turns out to be Hitler's. These unconscious reactions play a huge part in what we think of as decision-making. Conscious, deliberated actions – going somewhere on holiday, or taking a particular job – are similarly driven largely by unconscious processes, but they also involve activation of parts of the frontal lobes.

"Emotions are primarily bodily reactions – the feelings we call 'sadness' or 'joy' are just our conscious knowledge of physical changes that have already occurred"

As we have seen, some of the processes that occur here have that strange quality of consciousness, and the fact that we are aware of the grinding cognition involved in conscious decision-making tends to give us the illusion of controlling it. In fact, what we call 'decisions' may just be a special kind of awareness – the brain going about its continuous, complicated business of regulating, controlling and directing our bodies. **SF**

by **RITA CARTER**
Rita is a science writer and lecturer.

GETTY IMAGES

What makes you *you*?

Your brain is the most complex organ in your body – a mass of billions of neurons that keep you alive. But exactly how much do your genes and the outside world influence your little grey cells to shape your personality?

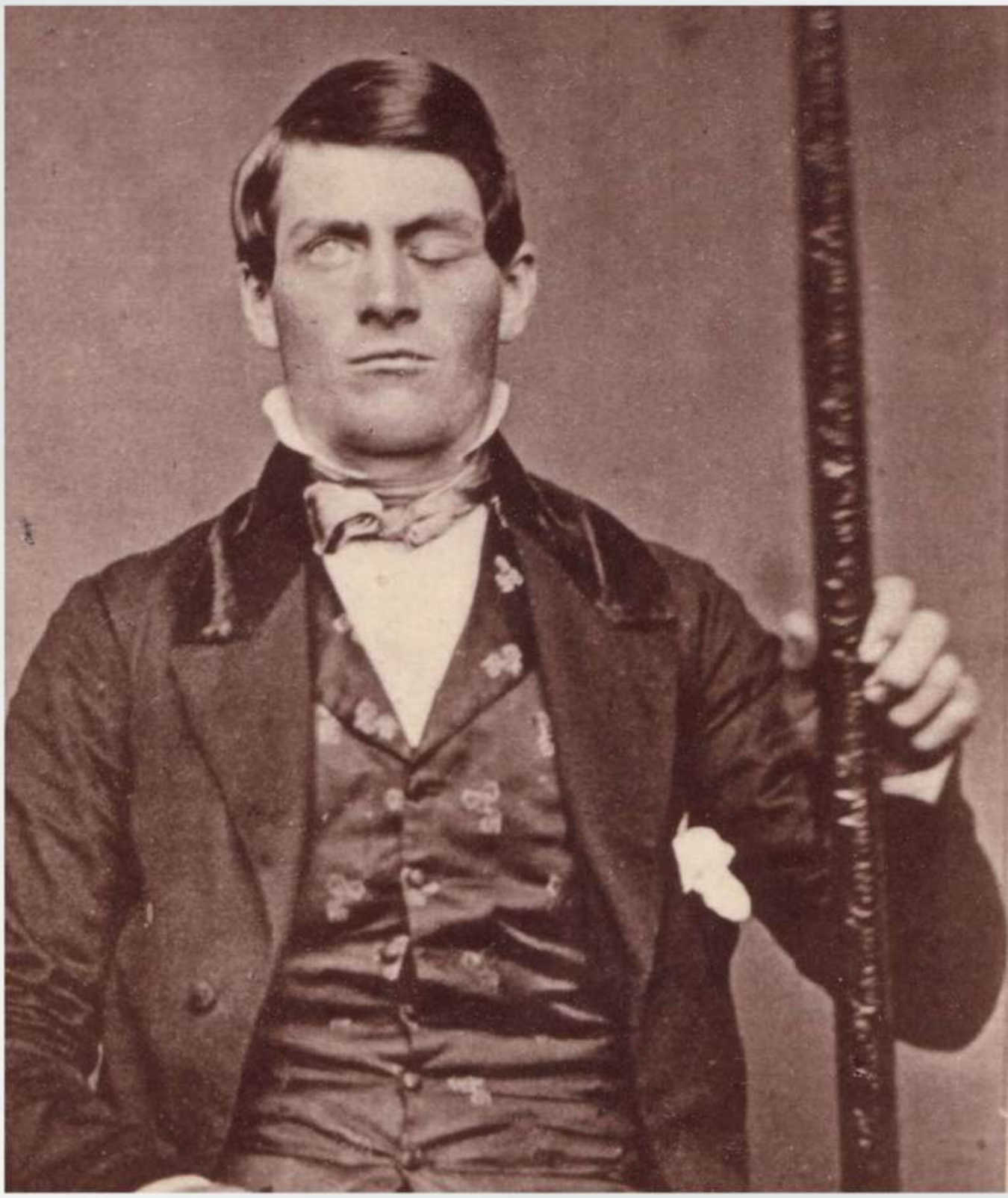
by RITA CARTER

One afternoon in 1848, on a railroad construction site in Vermont, a dynamite blast launched an iron rod into the air, which speared foreman Phineas Gage through the head. Incredibly, Gage survived but – deprived of a large part of his frontal lobe – his previously conscientious, agreeable personality did not. Gage became disinhibited, impulsive and rude.

Gage's story is familiar to every Psychology 101 student because it provided one of the earliest and most dramatic demonstrations of the physicality of human personality. It also demonstrated how easily and quickly it can be changed. Since Gage, it has become increasingly clear that the apparently 'essential' ways of thinking and behaving that identify each individual is a product of the functioning and structure of their brain. It has also become clear that you don't have to blow a hole in your head to change your personality. Brains are astonishingly plastic and, in some cases, all it takes to transform a person is a tiny electric current.

NO LAUGHING MATTER

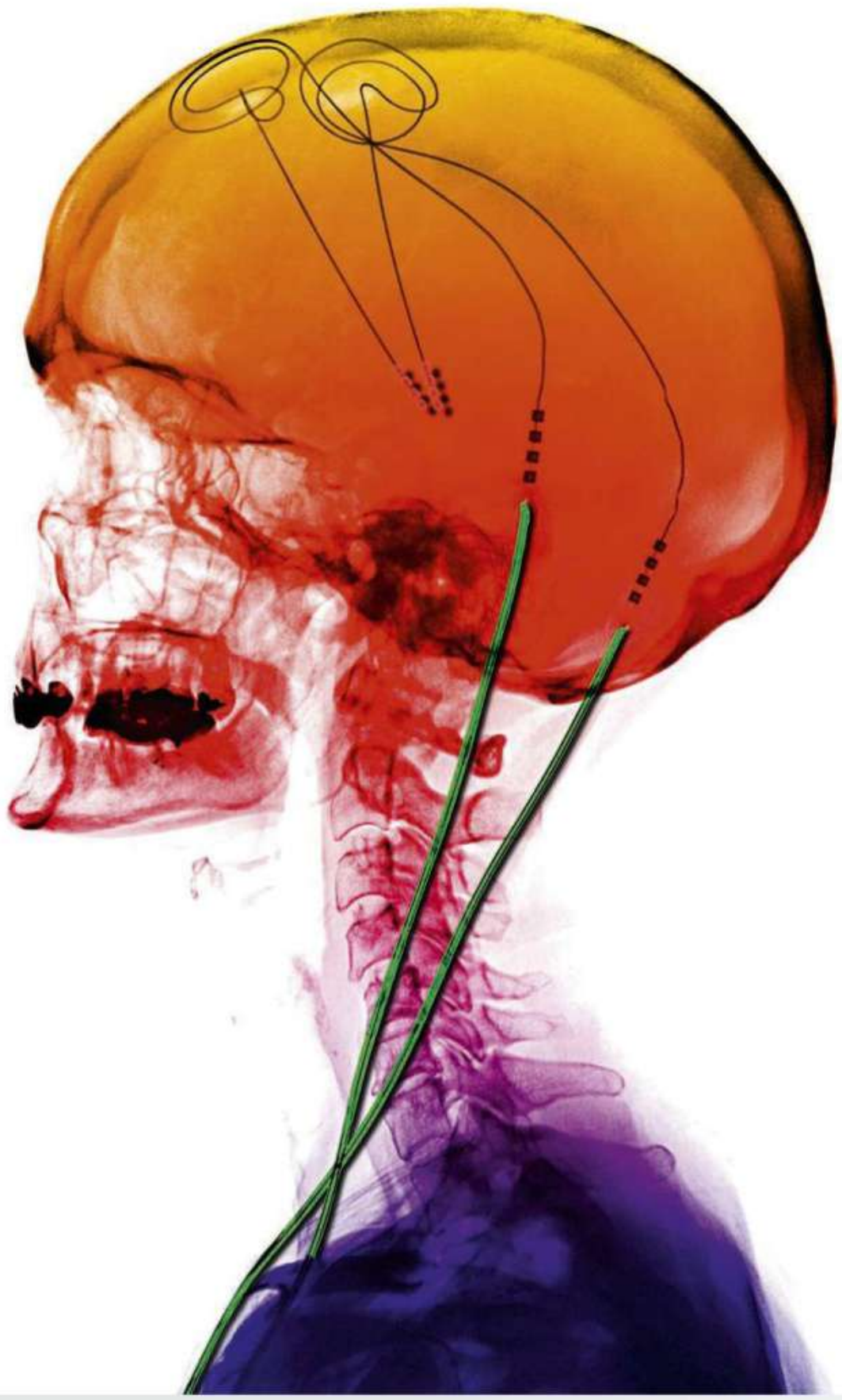
Edi Guyton is an American academic who, though professionally successful and surrounded by a loving family, has spent most of her life sunk in depression. Her first suicide attempt was at the age of 19 – she slashed her wrists. She tried to improve her outlook with drugs, ECT and years of talk therapy, but nothing made her smile. Her pessimism and joylessness were not linked to events, they seemed to be central to her personality.



ABOVE Phineas Gage holding the iron rod that drove a hole through his skull during a dynamite explosion

RIGHT Looking at emotional images triggers different brain activity in extroverts than in introverts

"EXTROVERTED PEOPLE HAVE MORE TISSUE IN THE AREA OF THE FRONTAL CORTEX CONCERNED WITH PROCESSING REWARD INFORMATION"



ABOVE A coloured X-ray showing deep brain stimulating electrodes being used to treat symptoms of Parkinson's disease

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Even the arrival of a cute grand-niece, Susan, didn't lift her spirits. "People would hand her to me and I would hold her and go through the motions," she says. "But I felt nothing."

Then, in 2007, Guyton completely changed – in a matter of seconds. This video clip (**bit.ly/deep_brain**) shows Guyton lying on an operating bed, fully conscious, surrounded by a team of surgeons. One of them has made a couple of holes in her skull and threaded two electrodes, connected to angel-hair wires, into a deeply buried region of her brain, known as Brodmann area 25. They ask Guyton what she is feeling. "Dread," she says. "Rate it," says one of the team. "Eight," says Guyton.

Then they turn on the power. "What's the dread now?" someone asks. "Three," she says. The surgeon makes a minute alteration to the position of the electrodes. Guyton makes an unmistakable sound. "She's laughing," someone says.

Later, Guyton told Dr Sanjay Gupta, the CNN medical correspondent who compiled the report: "Right there in that brain surgery I felt feelings that I thought were gone. I started thinking about holding and playing with Susan. It felt fantastic."

The effect has lasted – years later, Guyton remains transformed. Although she still has bad days, generally she is now a normal, cheerful person.

Deep brain stimulation is most commonly and successfully used to control tremors caused by burned-out dopamine circuits in the brains of people with Parkinson's disease. In addition to depression, though, it has had some success as a treatment for Obsessive Compulsive Disorder, which is caused by overactivity in brain circuits concerned with vigilance and other basic functions.

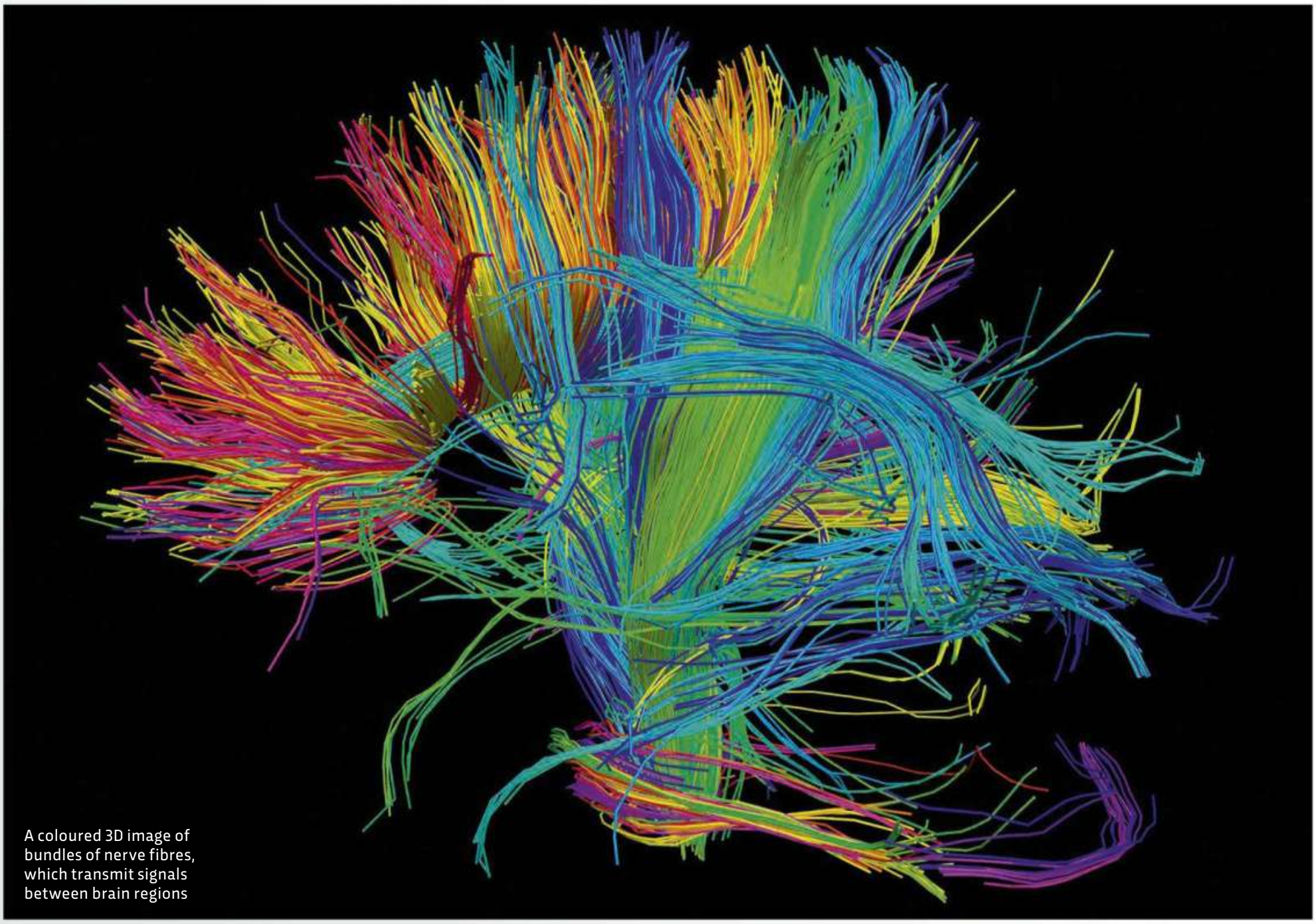
The technique is by no means a magic wand, because there are risks in the surgery, and brains are so complicated that what works for one person does not always work for another. Indeed, Guyton's operation was part of a trial that was in many ways a failure, with a problem-free success rate of less than 20 per cent. Nevertheless, Guyton's experience, and dozens of similar cases, demonstrate that even the most deep-seated behaviours can be changed by very small physical interventions.

MOULDING PERSONALITY

The fact that behaviour can be changed should not be surprising, because the correlation between brain function and personality has been demonstrated in hundreds of brain-imaging studies. Neuroscientists at Stanford University, for example, showed that people who are extroverts show quite different brain activity to introverts when shown emotional images. Another study showed that someone's personality is stamped on their brain, even when they are not actually doing anything. Yale researchers looked at the activity in various brain regions in 126 people while they let their minds wander, and measured how strongly the activity of each region compared to the activity in every other region. By doing this they created a personality pattern for each person, and found everyone was entirely distinct.

"MULTIPLE NEURONS FIRING IS A BIT LIKE A LINE OF DANCERS HIGH-KICKING THEIR LEGS IN SEQUENCE"

An illustration showing how nerve cells – neurons – are connected to each other by 'dendrites' (the green branches sprouting out of the main nerve bodies) and 'axons' (the orange rod-like structures)



A coloured 3D image of bundles of nerve fibres, which transmit signals between brain regions

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The team tested their discovery by working backwards from the patterns – they searched through scans from previous sessions to see if they could identify each person based on their pattern. They found they could pinpoint each participant with surprising accuracy, even among the twin volunteers who took part.

"The area of the brain where people differed most was the frontoparietal network – the parts that connect perceptions to the thinking and planning areas in the front of the brain," says Todd Constable, senior author of the study. "It's the most recently evolved part of the brain and the bit that makes humans distinct from animals."

Another researcher, Colin de Young, associate professor at the University of Minnesota, has found that the brain regions that are most concerned with behavioural features we regard as personality traits – for example, conscientiousness and extroversion – are measurably larger in people who score highly in those traits on an ordinary pencil-and-paper-personality test. Extroverted people were found to have more tissue in the area of the frontal cortex concerned with processing reward information. Agreeableness correlated with volume in areas that process information about the intentions of others. Neuroticism was linked with brain regions associated with threat, punishment, and negative affect. And conscientiousness scores matched the size of the prefrontal cortex – planning and voluntary control of behaviour.

GENES VERSUS TRAINING

It is impossible to say whether the distinctions noted by de Young are the cause or effect of the individuals' personalities. The structure of the brain is partly determined by genes, but brain areas are also built up by being used, in much the same way that muscles can be enlarged through exercise. Most likely it is the interaction of both genes and the way that people use their brains that create their distinctive structure.

Beneath the wrinkled cortex, the brain is made of a dense mesh of pathways that carries electrical currents from place to place. It is known as the 'connectome.'

The connectome is made of connective tissue that extends from each nerve cell

(neuron). When a neuron fires, it creates a pulsation, which suddenly changes the electrical potential. Each neuronal firing is a sort of mini-explosion and, if strong and frequent enough in one neuron, it kick-starts neighbouring cells, causing multiple neurons to begin firing at the same rate. It's like a line of dancers high-kicking their legs in sequence to create 'the wave'. These bursts of organised activity are our sensations, thoughts and emotions.

When neurons fire together they become temporarily bonded, so that in the future when one is activated it is more likely than before to trigger activity in the others. And if the initial 'dance' is particularly energetic, or performed frequently, the neurons that take part in it change physically. Their axons – the fibres that form the connectome – extend until they are close enough to their neighbours to create a new pathway between them. It's like the dancers linking hands. Axons shrivel if the path they form does not regularly carry messages. If the same neurons are stimulated to dance together time and again, though, the pathways between them become firmly entrenched as the electrical current passes repeatedly through them. The paths that carry most traffic become wider and more substantial, while those that are rarely used shrink.

You will see from this that the architecture of a person's brain is partly formed by what that person does – lose their temper, laugh, feel frightened, concentrate, and so on. The architecture so formed then encourages their brain to do the same things again and again. In behavioural terms it is called learning. Or, if you like, creating a habit.

"A PERSON'S BRAIN IS AFFECTED BY WHAT THEY DO – LOSE THEIR TEMPER, LAUGH, FEEL FRIGHTENED, CONCENTRATE, AND SO ON"

HABIT OF A LIFETIME

Much of an individual's personality is simply an accretion of habits. If a person is in a job where being conscientious is necessary or rewarding, this trait may become central to their personality, even if their genetic inheritance may have inclined them towards carelessness. The sooner such environmental influences are felt, the more impact they have, because young brains are more easily changed than old ones. Indeed, nurture starts to have effects on personality even before birth.

An unborn child may have genes that would incline them to be serene and laid back, but if the mother happens to be under great stress during pregnancy, the cortisol in her blood can pass to the foetus's brain and stimulate neurons in the developing amygdala – the brain nucleus that generates emotions. The resultant 'dancing' of amygdaloid neurons during gestation could strengthen the pathways carrying signals from the amygdala, and prime the child to be fearful for the rest of their life.

This mechanism is how identical twins can have entirely different personalities. There are no single genes *for* personality traits, such as conscientiousness or extroversion, but variations in the ways genes work in concert determine how much of these characteristics an individual is likely to manifest. Identical twins share gene variations, but as soon as they have split into two individuals they are subjected to slightly different environmental stimuli. Even being in different positions in the womb has an effect – one child may receive more or less hormones, for example, another may hear more of the outside world, or feel bumps on the mother's body more easily. These apparently minute differences can have profound effects on developing brains, such that by the time the twins are born they may already be startlingly different. If you could see the surface of their brains beneath their skulls you would be able to discern that the shapes of their wrinkles and bumps is different.

As they grow into toddlers the differences become more obvious. Outside the confines of the uterus an infinite variety of experiences are available, and the two infants will interact slightly differently with the world at every turn. The cumulative effect of these minuscule differences may end up being enormous. Take for example, autism. The condition is now known to have a strong genetic component, but it does not necessarily develop in a child with an autism-prone genome. Tiny environmental influences – too random and minute for anyone to predict or control – can offset genetic inheritance. Hence, there is about a

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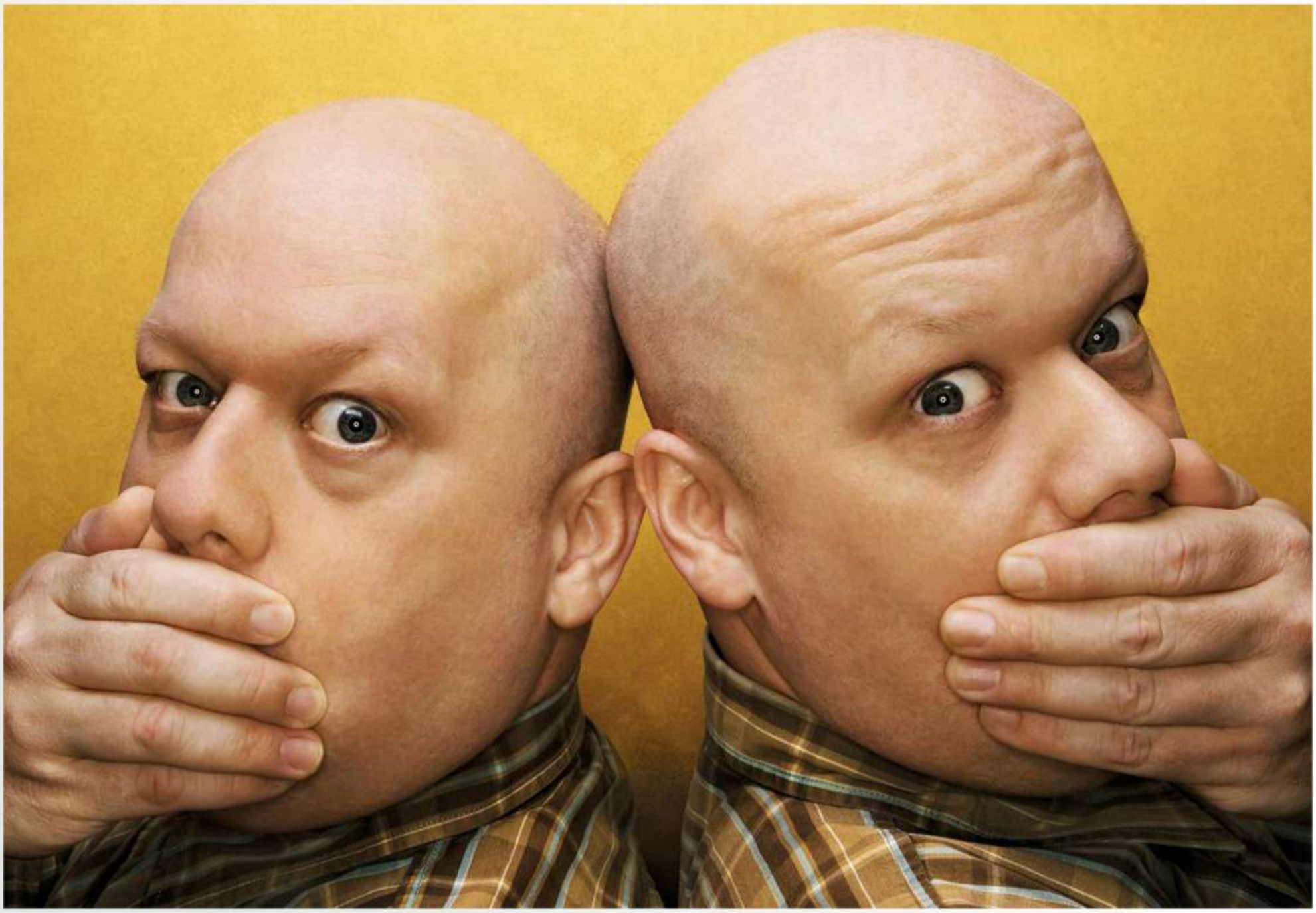


Exposure to slightly different environmental stimuli in the womb means that, from an early age, the brains of identical twins develop in different ways

one in three chance that, though one twin is autistic, their identical brother or sister is not.

EPIGENETIC FACTORS

Things get more complicated as the children grow up. As their experiences become ever-more diverse, the once-identical DNA in the twins' cells starts to differ. The actual genes remain the same, but differences in environmental factors, such as illness, trauma, or exposure to toxins causes chemical changes to take place in and around the DNA thread – so-called 'epigenetic changes' – which alter the way that the genes are activated, or 'expressed.' Hence, by adulthood the twins are effectively different genetically. Although they may still exhibit many similarities in character, their personalities will necessarily be different, because they will have developed physically different brains.

SELF-TRANSFORMATION

As well as genetic fortune and random environmental influences, personality can be moulded deliberately, which is good news as most people are unhappy with at least one aspect of their personality. A vast counselling and self-help industry has grown up to serve this purpose, helping people address everything from their rage and assertiveness, to their capacity for self-forgiveness.

Although traditional methods of self-transformation are likely to be lengthy and difficult, it seems they can work. In one study researchers found that participants were able to make significant personality changes within four months. For example, people who wanted to be more extroverted tested as being higher in extroversion by the end of the study period. Along with changes in how they responded to personality testing, they also reported significant changes in their behaviour, which matched the personality changes they desired.

So, take no notice of those who claim 'you can only be yourself.' With enough time, effort, and determination you can be more like the person you want to be. **SF**

by **RITA CARTER**
Rita is a science writer and lecturer.

GETTY IMAGES

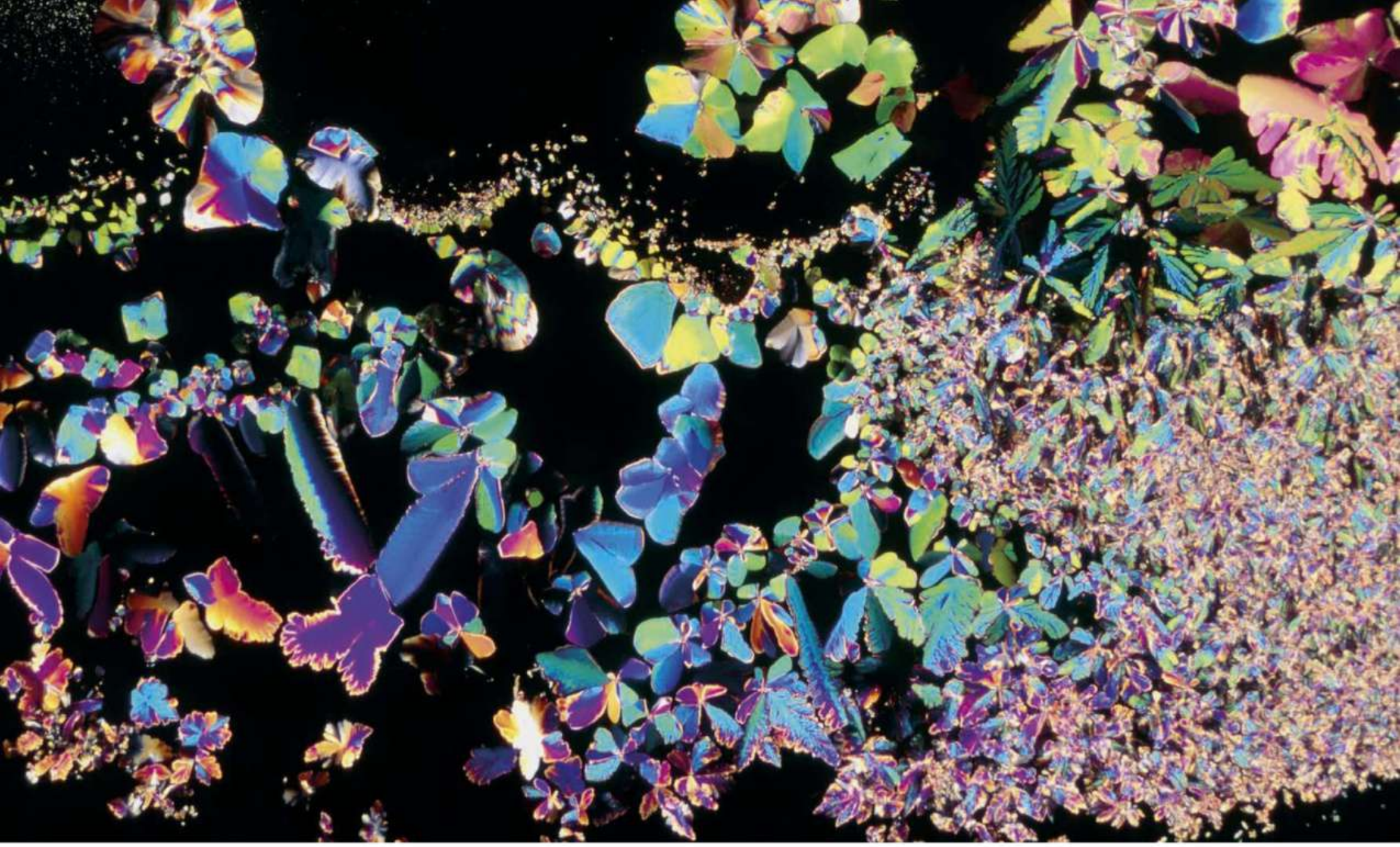
THE HIDDEN POWER OF YOUR BRAIN

The way you think about life can fend off infection, help you live longer and even spare you from the surgeon's knife

by ANDY RIDGWAY

Nobody likes catching a cold. But it seems that we have a pretty effective way to reduce our chances of getting one – being happy. In a study published in 2003, over 300 volunteers in the US were knowingly infected with a virus responsible for the common cold. They were then monitored for symptoms over the next five days. The results were clear. Those with the most positive outlooks on life were three times less likely to develop cold symptoms than those who were the least happy. Other studies have also reached similar conclusions.

A positive mental attitude can have long-term health benefits too. In the US, the autobiographies of 180 Catholic nuns were analysed by psychologists to see what they revealed about their personalities. It showed that those who were positive and happy tended to live 7 to 10 years longer than those who weren't.



In spite of such studies, the influence of our mind over our health has left some members of the medical community decidedly sceptical. But there's a growing body of research showing that what goes on inside our heads has a direct influence over how healthy we are. Not only that, our thoughts can even help cure us of some ailments. Importantly, researchers are now starting to understand more about the mechanisms at work, and how our thoughts are connected to our physical health.

STAY POSITIVE

A researcher at the forefront of this field is Dr Laura Kubzansky, co-director of the Center for Health and Happiness at Harvard School of Public Health. One of her most recent studies involves just over 70,000 nurses in the US. In the research, she discovered that those who are the most optimistic have roughly 15 per cent longer lifespans than those who are the least optimistic.

In part, it is thought that these differences in longevity are down to the fact that those with positive attitudes tend to do more exercise and smoke less. But it is not just that. "People with higher levels of positive emotions do a better job of managing stress," explains Kubzansky. "So a lot of the stress-activated biochemical processes, like higher levels of cortisol that are circulating and driving inflammation, are less likely to occur." Reduced stress also reduces the 'allostatic load', the medical term for the general wear and tear on the body, such as strain on the internal organs, that occurs when a person is under long-term stress.

"People with higher levels of positive attitudes do a better job of managing stress"

ABOVE The hormone cortisol, seen here in a microscope image taken with polarised light, is released in response to stress. High levels over long periods of time have a negative effect on health

But, says Kubzansky, this is likely to just be part of the picture. There will be other biochemical processes within our cells that are influenced by our positivity that we're not aware of yet. Part of the problem is that medical research has been understandably focused on getting a handle on what's going on in our bodies when we're ill, rather than when we're feeling well and things are going right. "We're not very good at looking at the biology of good functioning, we mostly just look at the biology of normal or bad," she says. "But the time for positive biology has come."

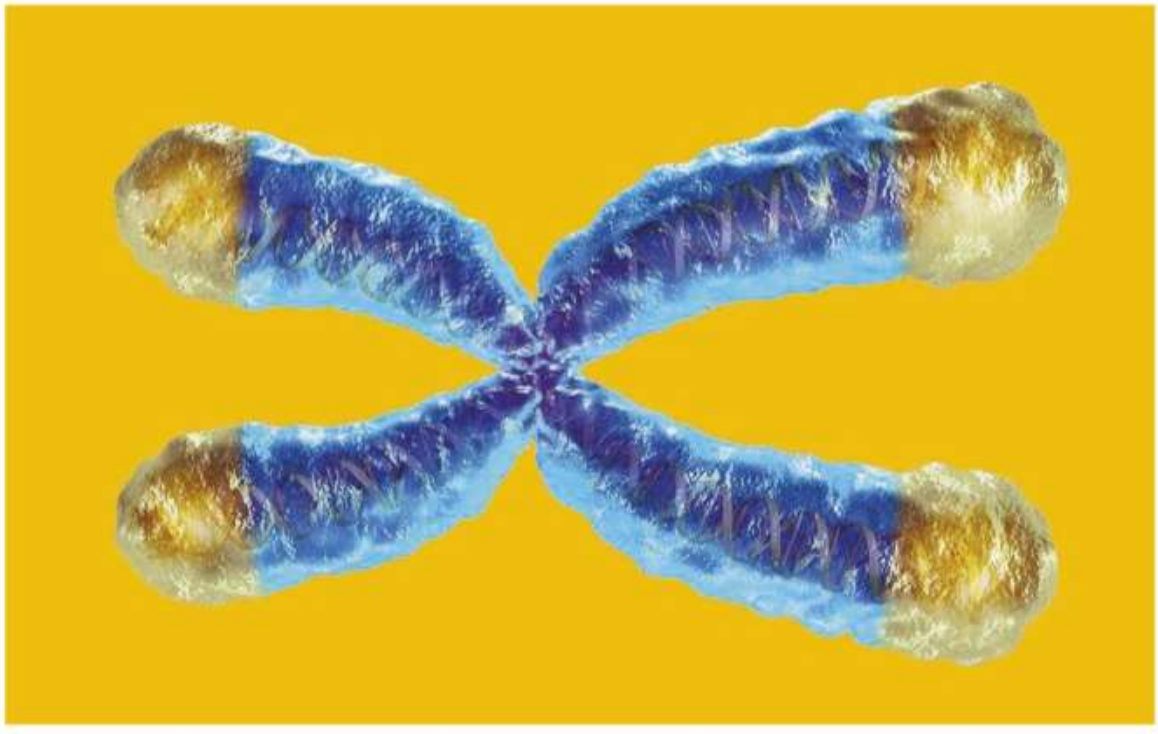
One of Kubzansky's priorities now is to look at how our microbiome – the bacteria and other microorganisms that live inside our bodies, particularly in the gut – are influenced by how positive we are. "There is some preliminary research that links depression to alterations in the gut microbiome,

so it's logical to speculate that you might get effects in the other direction," says Kubzansky. The effect of our mental state on the microbes inside us is a big deal because the health and make-up of these microbes has been linked to several aspects of our physical health, such as whether or not we're overweight.

TRICKING THE TELOMERES

There's already evidence that the way we think can influence our DNA. For over a decade now, the laboratory of molecular biologist Dr Elizabeth Blackburn at University of California, San Francisco, has been investigating the influence of our state of mind on our telomeres, the chunks of DNA that act as protective caps at the end of chromosomes. Telomeres get shorter each time a cell divides and if they get too short, the cells in which they are located no longer divide and so they die. Short telomeres have been associated with everything from heart disease to lung conditions. Blackburn was awarded the Nobel Prize in 2009 for her research on telomeres and telomerase, an enzyme that fights against the tendency of telomeres to get shorter over time.

Blackburn's lab first looked at the telomeres of mothers who were caring for children with long-term health conditions. They found that the longer the mother had been looking after the child – and so under more stress – the shorter her telomeres. "It was striking," says Blackburn. After that, they investigated other potential influences of the mind on DNA. It seems that, on average, pessimists have shorter telomeres than optimists. And being cynical isn't good for your long-term health either. In one study on more than 400 British ➤



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BELOW Protective telomeres (yellow) can be seen on the ends of this chromosome (blue)

THE ETHICS OF PLACEBO SURGERY

Sometimes there's no substitute for surgery, but what if a placebo was as effective?

The mind plays a big role in how effective surgery is. One study, published in the *British Medical Journal*, combined the results of more than 50 surgical trials that compared a widely used surgical technique, such as cleaning out painful knee joints with salt water, with a placebo surgery. It showed that in 74 per cent of the studies, patients who had the placebo surgery showed signs of improvement, while in 51 per cent of the trials, placebo surgery was as effective as the real thing.

Few would doubt the importance of using placebo surgery to test existing surgical techniques. But given that placebo surgeries do seem to work, isn't there a case for using them as a treatment in their own right? "Fake surgery is not benign; it's not a sugar pill," says Dr Ted Kaptchuk of Harvard Medical School. "It has real costs and dangers." So placebo surgery can't be justified ethically, he says. But 'open-label placebo' medication, where patients are told that their pill, medicine or cream doesn't contain an active ingredient, is justifiable, he says. The other approach to harnessing the power of the brain, says Kaptchuk, is to use 'conditioning'. Here, the body is tricked by pairing a known treatment, such as the painkiller morphine, with something that has no effect, like saline solution. If the two are injected together, eventually when the saline is injected on its own, it has the same effect as that of a painkiller.

CAN WE MEASURE HAPPINESS?

Finding a smile scale: the search for a metric with which to quantify someone's happiness

If being happy is good for your health, helping you to fight off a cold and even prolonging your life, what is happiness? We know when we feel happy, but can we actually detect happiness?

Dr Mark Holder, an associate professor of psychology at the University of British Columbia in Canada, decided to find out. "I had conceptualised happiness as the opposite of depression; so if you think of a continuum, the more you move away from depression, the happier you are." So he asked some of his students to provide him with saliva and urine samples and he measured levels of two hormones – cortisol and serotonin. After all, antidepressant drugs are designed to increase serotonin levels, and high levels of cortisol have also been linked to depression. The trouble was, neither cortisol nor serotonin levels in the students' samples showed any relationship with how happy they were. "It tells me that my initial conceptualisation of happiness was wrong," says Holder. In other words, happiness and depression can't be thought of as opposites along the same spectrum. He didn't give up, though. "We looked at some putative biomarkers," he says. "That's a fancy way of saying, I took some guesses." Next, he measured neural growth factors (NGFs), proteins that control the growth of nerve cells. Again, he drew a blank. "We haven't been able to unravel the biochemistry of happiness," says Holder.

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civil servants, they found that those who showed higher levels of cynical hostility towards others – and so were more likely to answer 'yes' to the question 'most people make friends because friends are likely to be useful to them' – had shorter telomeres.

But how can the way we think affect our DNA? For starters, when we're stressed over long periods of time, levels of the hormone cortisol go up. "We know that higher cortisol dampens down the replenishing action of telomerase," says Blackburn. The good news is that we can boost our telomerase levels. In one study Blackburn was involved with, 30 volunteers spent three months at a retreat in Colorado meditating for six hours a day. By the end, levels of telomerase in their cells were one-third higher compared to another group who did not go on the retreat. It is thought that the telomerase boost wasn't specifically down to meditation – it was more due to the increased sense of wellbeing the volunteers had. So anything that increases the sense of wellbeing is likely to have the same effect.

PLACEBO EFFECT

When it comes to the influence of our minds on our bodies when we're ill, the most widely known phenomenon is the placebo effect. Here, when someone takes medication that has no active ingredient, such as a sugar pill, it can do anything from numbing headaches to relieving the symptoms of colds. It all comes down to believing the medication will help. Examples of placebo treatments have been documented for centuries, but more recent research has provided some intriguing insights. For example, in one study in Italy, a placebo tranquilliser was better at soothing patients' nerves before an operation if it was blue – or at least that was the case with female patients. Orange pills were most effective with the men.

The placebo effect plays a role when we have surgery too. Some common surgical techniques have been tested against 'placebo surgery', where a patient thinks they are having full-blown surgery, but in fact they may just have an incision in their skin or some other minor procedure. In many studies, the placebo surgery has been just as effective as the real thing. Research such as this is typically used to question whether certain surgical procedures should take place at all. But some scientists say that we've been thinking about the placebo effect in completely the wrong way. It's not something to just test a surgical technique or a drug against, we should actually start to use it to treat patients.

"The placebo effect has been recognised for centuries – at worst it's been viewed as a villain or a threat to medicine, such as when a new drug that developers have spent billions [perfecting] gets beaten by a mere placebo," says Dr Alia Crum, a principal investigator at Stanford University's Mind and Body Lab. "But there is huge potential for it to be used for good."

It's a point Crum makes in a TED talk about the placebo effect. She describes one of her experiments where a placebo cream with no active ingredients could be used to clear up allergic rashes. However, she notes this was only when the doctor was warm and friendly, and showed signs that they were good at their job, such as wearing a badge saying 'Fellow at the Stanford Allergy Center'.

"Our research shows that the placebo effect is alive and at play in every single medical encounter," she says. According to Crum, we just need to train doctors to think about what they do and say in front of patients, in order to harness the placebo effect more effectively.

In most placebo studies, each volunteer is told they will either receive the real treatment or a placebo. But Dr Ted Kaptchuk, a placebo researcher at Harvard Medical School, decided to actually tell volunteers he was going to give them a placebo pill for irritable bowel syndrome. "Every placebo researcher in the world said, 'Ted, you are crazy'," he says. But bizarrely, it still worked. The patients said their symptoms improved by 60 per cent. "In fact, it's consistently worked in nine studies," says Kaptchuk.

It undermines one of the common explanations of why a placebo works – that patients think they are getting the real treatment and so it works because they expect it to. Kaptchuk says that many of the patients who come to him for trials of these so-called 'open-label placebos' have tried many other treatments for their condition that haven't worked, and that their hope and uncertainty seem to play a role. Kaptchuk also says placebos tend to be most successful with conditions that have a big psychosocial component, where mental factors and perceptions are involved, such as chronic pain.

"Open-label placebo doesn't get rid of malaria and doesn't lower cholesterol," he says.

"Our research shows that the placebo effect is alive and at play in every single medical encounter"

While we still don't quite understand the psychology behind the placebo effect, there's no doubt that it has an influence on the body. In research on placebo painkillers, for example, when neurotransmitters such as endorphins and dopamine are blocked, the placebo effect is stopped too.

POWER OF THE MIND

The healing power of the mind doesn't stop at the placebo effect. In his famous experiment, Russian physiologist Ivan Pavlov conditioned dogs to salivate when they heard a sound, such as the ticking of a metronome, if they first heard that sound several times when being fed. Similar 'training' could be used on patients too.

Studies have shown that when a medical treatment is paired with something else, such as a sweet or a smell, that something else can produce the same effect as the medicine after a while. In one study in Germany, for example, this technique enabled volunteers' bodies to produce natural killer cells – cells that are part of the immune system – in response to a sherbet sweet. The idea is that in the future, the bodies of patients could be trained to subdue pain, fight infections or calm allergies by conditioning. Eventually, long-term medication may not be needed.

All of this research points towards a future where we actively use our minds play to influence our health, both when we're well and when we're sick. But there's a big-money question; how much can we actually change our mindset anyway? "It's not easily modifiable," says Kubzansky. "I don't think somebody one day says, 'I'm going to be more optimistic today'. If it was that easy, we'd all be living in a utopian society. But I do think it's modifiable with some focused attention." When it comes to harnessing the power of the mind with regards to medical treatments, it seems there's still work to be done in order to change the mindsets of some in the medical community. "The question is, how do you move the system?" says Kaptchuk. "Sometimes it's science, sometimes it's will, and sometimes it's the imagination." **SF**

by **ANDY RIDGWAY** *(@andyridgway1)*
Andy is a freelance science writer based in Bristol.

What if you could wipe out a painful moment from your past, implant a new memory, or easily remember everything for an exam? Soon, science will be able to shape your memories…

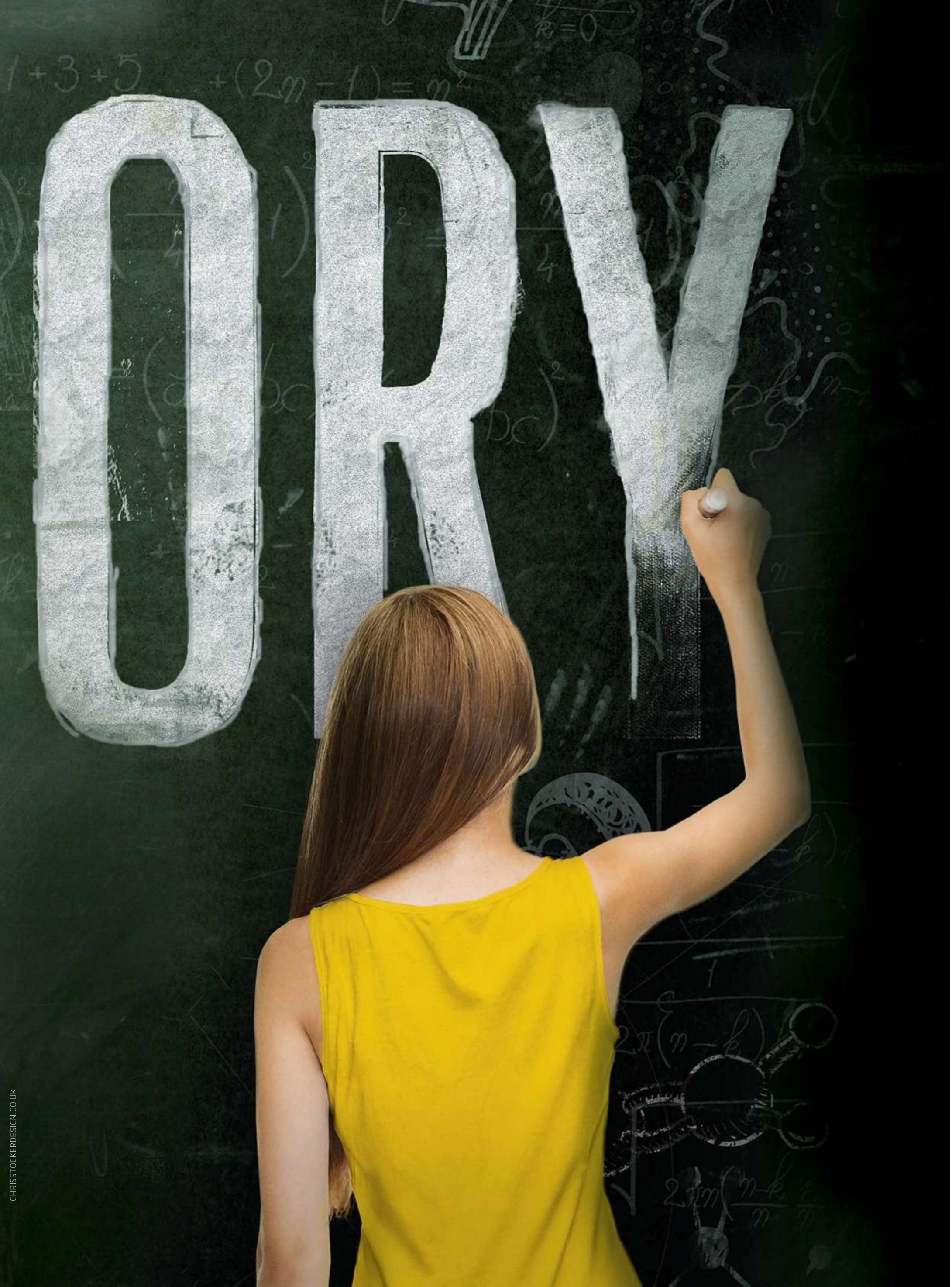
by NICOLA DAVIES

Ever wished you had a better memory so you were able to recall names, dates and faces more easily, or even get better grades in exams? How about removing all recollection of a failed relationship like the characters in Michel Gondry's Academy Award-winning movie *Eternal Sunshine Of The Spotless Mind*? Or virtually travelling the Solar System via false memories implanted directly in your mind like Arnold Schwarzenegger's Douglas Quaid in the sci-fi classic *Total Recall*?

Well, 'therapies' such as these may be coming sooner than you think, as scientists have been making great strides in how to delete, improve and even create memories.

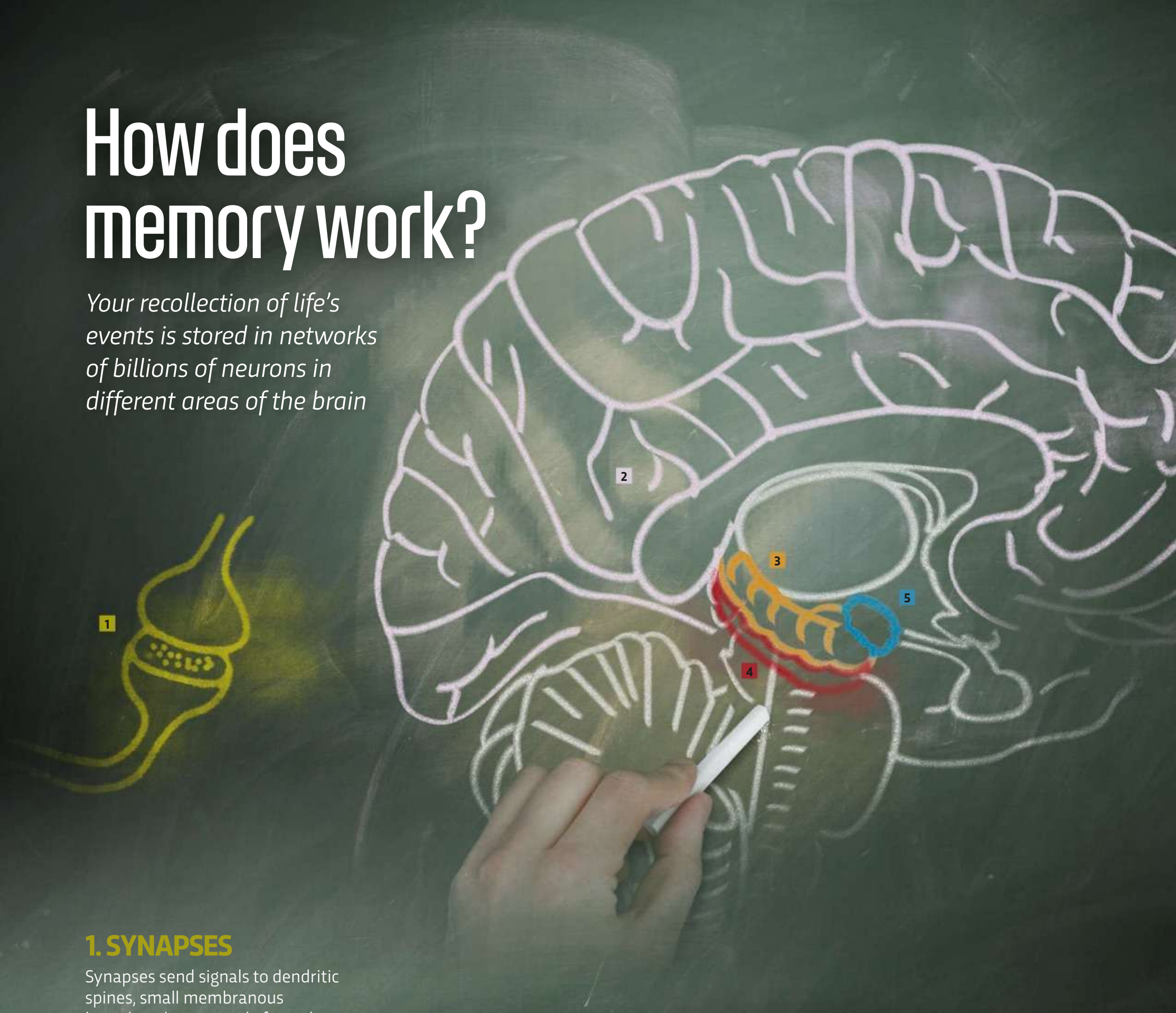
"Memory is a very important aspect of cognition," says Dr David Vauzour, a research fellow at the University of East Anglia. "It refers to what you can remember, along with the capacity for remembering. Some memories are retained for a short period of time and then discarded, but important ones are stored in the brain and can be retrieved at will. This process of learning new information, storage and recall, involves a complex interplay of brain functions."

It is this complex network of nerves and chemical processes that will shed light on how the human brain stores and recalls memories, before we are eventually able to figure out exactly how to manipulate them.



How does memory work?

Your recollection of life's events is stored in networks of billions of neurons in different areas of the brain



1. SYNAPSES

Synapses send signals to dendritic spines, small membranous branches that protrude from the dendrites at a neuron's end. It is in these spines that memories are thought to be stored. Research on mice has shown that the learning process creates new synaptic connections.

2. CEREBRAL CORTEX

Memories are stored in complex networks, primarily in the cerebral cortex, the outermost layer of neurons in the brain. Long-term memory can be divided into two major categories: declarative and implicit memory. Declarative memory requires a conscious effort to recall, while implicit memory, such as procedural memory, refers to skills and routines.

3. HIPPOCAMPUS

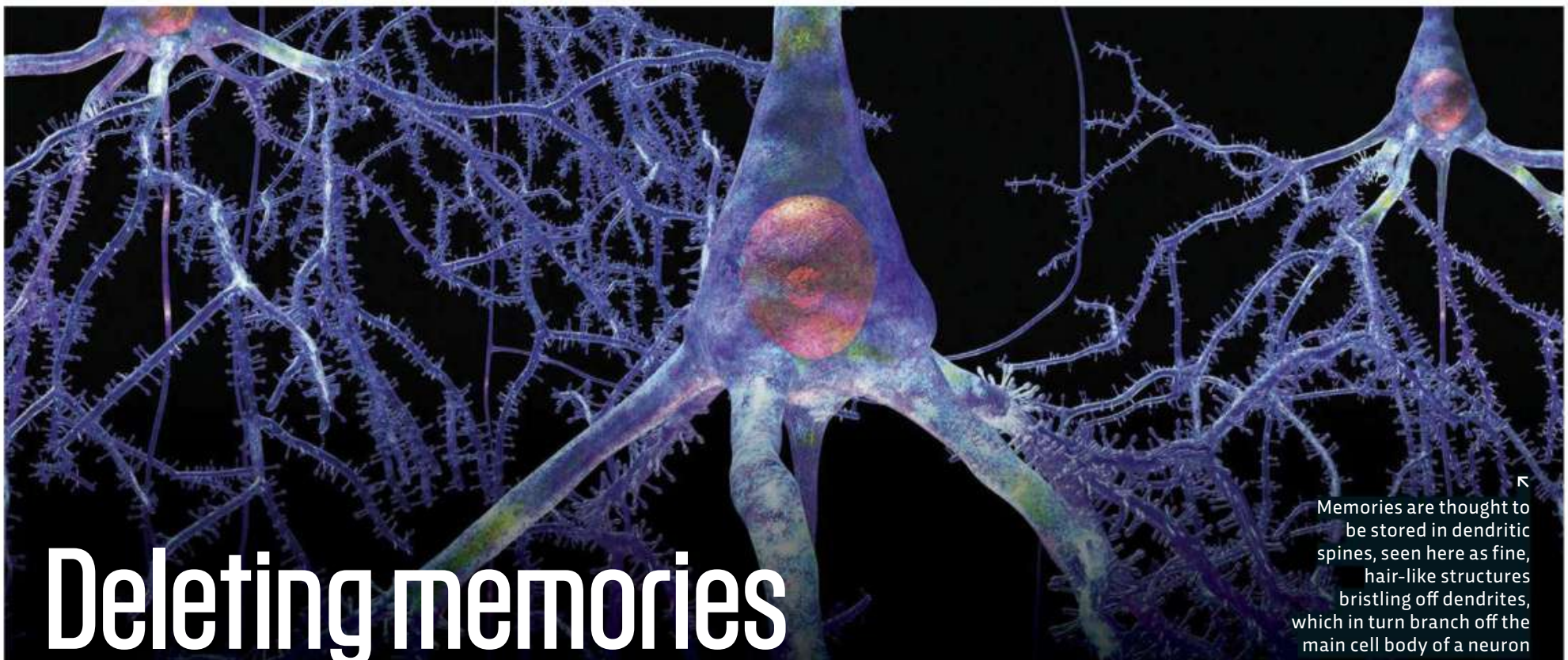
Crucial to both spatial awareness and memory, we have one hippocampus on each side of the brain. "Long-term memories are likely formed by a variety of different mechanisms depending on the type of memory," says Dr Michael Yassa of the University of California. "There is evidence supporting the notion that long-term memories for facts and events are stored initially using the hippocampus, but eventually most memories become stored as a distributed representation throughout the brain. The process is likely some form of strengthening of communication among neurons."

4. ENTORHINAL CORTEX

Involved in consolidating memories, particularly spatial memory, the entorhinal cortex acts as a gateway between the memory-forming hippocampus and neocortex, which deals with sensory perception.

5. AMYGDALA

The two walnut-shaped amygdalas are clusters of neurons that deal with emotion and fear. A 2013 study led by Dr Haohong Li and Dr Mario Penzo and published in *Nature Neuroscience*, announced that the specific part of the amygdala that encodes fear memory had been pinpointed – it's called the 'lateral subdivision'.



Memories are thought to be stored in dendritic spines, seen here as fine, hair-like structures bristling off dendrites, which in turn branch off the main cell body of a neuron

Deleting memories

While memories can be a source of great pleasure, they can also be a source of great pain. So imagine being able to get rid of them

People with post-traumatic stress disorder (PTSD) constantly relive traumatic memories. Similarly, drug addicts connect certain habits with the sensation of being high, which stimulates their craving. By removing or subduing specific memories, traumatic emotions and harmful behaviours can be prevented.

So, how do you delete memories? "Researchers have used a three-stage model to describe how the brain learns and remembers, with impairment in any of these processes resulting in memory failure: acquisition, consolidation and retrieval," says Dr David Vauzour, a senior research fellow at the University of East Anglia.

One attempt to delete memories, conducted by Marijn Kroes and his colleagues at Raboud University Nijmegen in the Netherlands, focused on the consolidation process. Memories are periodically rewritten in the mind, or reconsolidated. But electroconvulsive therapy (ECT) appears to either prevent memories from being rewritten, or alters them during the reconsolidation process. In the team's 2013 study, published in *Nature Neuroscience*, participants undergoing ECT for depression were shown a troubling story in words and pictures. A week later they were reminded about it and given ECT. This completely wiped out their recall of the distressing narrative.

Similar breakthroughs have also been made using the chemical approach. A 2013 study, led by Dr Courtney Miller of the Scripps Research Institute in San Diego, sought to help methamphetamine addicts by targeting the removal of memories linked with drug use.

"What makes this finding so exciting is that the inhibitors seem to be incredibly selective as to the memory type," says Miller. "We think we're able to selectively target drug-associated memories, and hopefully traumatic memories in the future, because the brain is using a different mechanism to store them."

Subsequent research, published in *Cell* in January 2014, reveals that drugs known as histone deacetylase inhibitors (HDACIs) can enhance the brain's ability to permanently replace old traumatic memories with new memories. In the first phase of the study, carried out at the Massachusetts Institute of Technology (MIT), mice were exposed to a tone followed by an electrical shock. Once the mice learned to associate these two events, they began to freeze in fear upon hearing the tone, even when they did not receive a shock. The researchers then presented the tone without the shock to test whether the mice could unlearn the association. This was successful for mice exposed to the tone-shock pairing one day earlier, but not for mice that formed the traumatic memory one month earlier. These mice were then given HDACIs before undergoing the 'unlearning' exercise. The mice then stopped freezing in response to the tone.

"Electroconvulsive therapy appears to prevent memories from being rewritten, or alters them"

THE GENETIC COMPONENT

Delving deeper, the researchers from MIT have discovered a gene essential for 'memory extinction', called TET1. Their findings show how boosting TET1 activity might benefit PTSD sufferers by making it easier to replace fearful memories with more positive ones.

Researchers had two sets of mice develop a fear of a cage by electrocuting them inside it. The mice were then put into a cage without being electrocuted. Those with an inhibited TET1 gene no longer feared the cage, because the fear memory was replaced with a positive one; a new memory of not being electrocuted.

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Memory boost

Your recollection of life's events is stored in networks of billions of neurons in different areas of the brain

In the Leonardo DiCaprio film *Inception*, professional criminals use an experimental military technology to implant ideas and memories into a victim's mind while they sleep.
The concept may seem far-fetched, but false memory implantations happen all the time, including when people are awake. What's more, they can have drastic consequences, especially in court trials where juries place a disproportionate amount of credibility on eyewitness testimony.

Every one of us is susceptible to false memories, even those with otherwise exceptional powers of recall. This was shown in a 2013 study led by Lawrence Patihis, then at the University of California, Irvine, now an assistant professor at the University of Southern Mississippi. Patihis compared 38 'control' individuals with 20 individuals who had a highly superior autobiographical memory, in other words, the ability to remember personal experiences as well as more general facts and knowledge. Despite it being likely that the latter group might be immune to memory distortions, the opposite was found. Over a two-week period, a series of exercises designed to test participants' susceptibility to forming false memories were administered. In each case, false memories were apparent just as often in those with superior memory as in controls. For example, when presented with a word list that included 'thread', 'knitting', and 'pin', both groups were likely to later 'remember' also having seen 'needle', which was never shown.

More recently, Nobel Prize winner

Prof Susumu Tonegawa was able to successfully implant fear memories in mice. Tonegawa and his team genetically engineered mice to express channelrhodopsin-2 (ChR2), a protein in neurons associated with memory formation and storage in the hippocampus.

IMPROVING MEMORY

Kim Peek, the 'megasavant' who was the

FEAR FACTOR

How scientists induced false memories in mice

1 A mouse was put in a blue box and the neurons responsible for memorising the environment were labelled. These neurons were then made responsive to light.

2 The mouse was then put in a red box and a light was switched on to activate the previously labelled cells, so it recalled the first box. The mouse was then given small electric shocks.

3 When the mouse was returned to the blue box, it showed signs of fear, revealing how it had formed a false fear of the first box, where it was never shocked.

LEFT The 'megasavant' Kim Peek was able to memorise everything he ever read

inspiration for the multiple-Oscar-winning film *Rain Man*, could remember almost everything he had ever read. He could also read both pages of a book simultaneously and retain the information. While we might all love to be like Peek, there are several effective ways of improving your memory.

"Physical health, emotional state, stress level and diet exert a big influence on how well you learn and remember," explains Dr David Vauzour, a research fellow at the University of East Anglia.

One study at the University of Alabama, Birmingham, published in the *Journal Of Neurology* in 2013, revealed that those who more strictly adhered to a Mediterranean diet were less likely to develop problems with their memory. In another study, led by Dr Yves Sauvé of the University of Alberta, Canada, it was shown that high levels of omega-3 in a person's diet can help to improve the communication of the neurons used for memory.

"Since 'smart drugs' are prescription medications, the long-term effects are unknown and potentially dangerous"

Evidence suggests that exercise is also key to a healthy memory. Research led by Dr Sandra Chapman of the University of Texas at Dallas in 2013, showed that aerobic exercise – also known as cardio – improves memory by helping maintain consistent and healthy blood flow to the hippocampus.

There are some people, however, who baulk at the thought of putting on their running shoes and hitting the pavement, and would instead prefer to simply swallow a memory-improving pill. This attitude has led some students wishing to stay alert and retain memory during exams to turn to so-called 'smart drugs'. Modafinil, Ritalin, and Adderall are frequently sold on the black market. But since these are prescription medications for conditions that most students do not suffer from, such as narcolepsy and ADHD, the long-term effects are unknown and potentially dangerous.

Moreover, they may not even have the expected effect of improving memory. Although they can give the user the impression of a temporary memory boost, a placebo-controlled trial, led by Irena Ilieva when she was at the University of Pennsylvania, showed no improvement in the performance of young adults taking Adderall compared to those taking a placebo. So it would appear that pills do not provide a quick-and-easy shortcut to improving memory. **SF**

by **DR NICOLA DAVIES**
Nicola is a health psychologist and writes for BBC Science Focus.

Aerobic exercise improves memory as it helps to maintain a healthy blood flow to the hippocampus

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TRICKS OF THE MIND

Psychologists are starting to figure out why we get false memories and as it turns out, they might even be useful…

by PHILIP BALL

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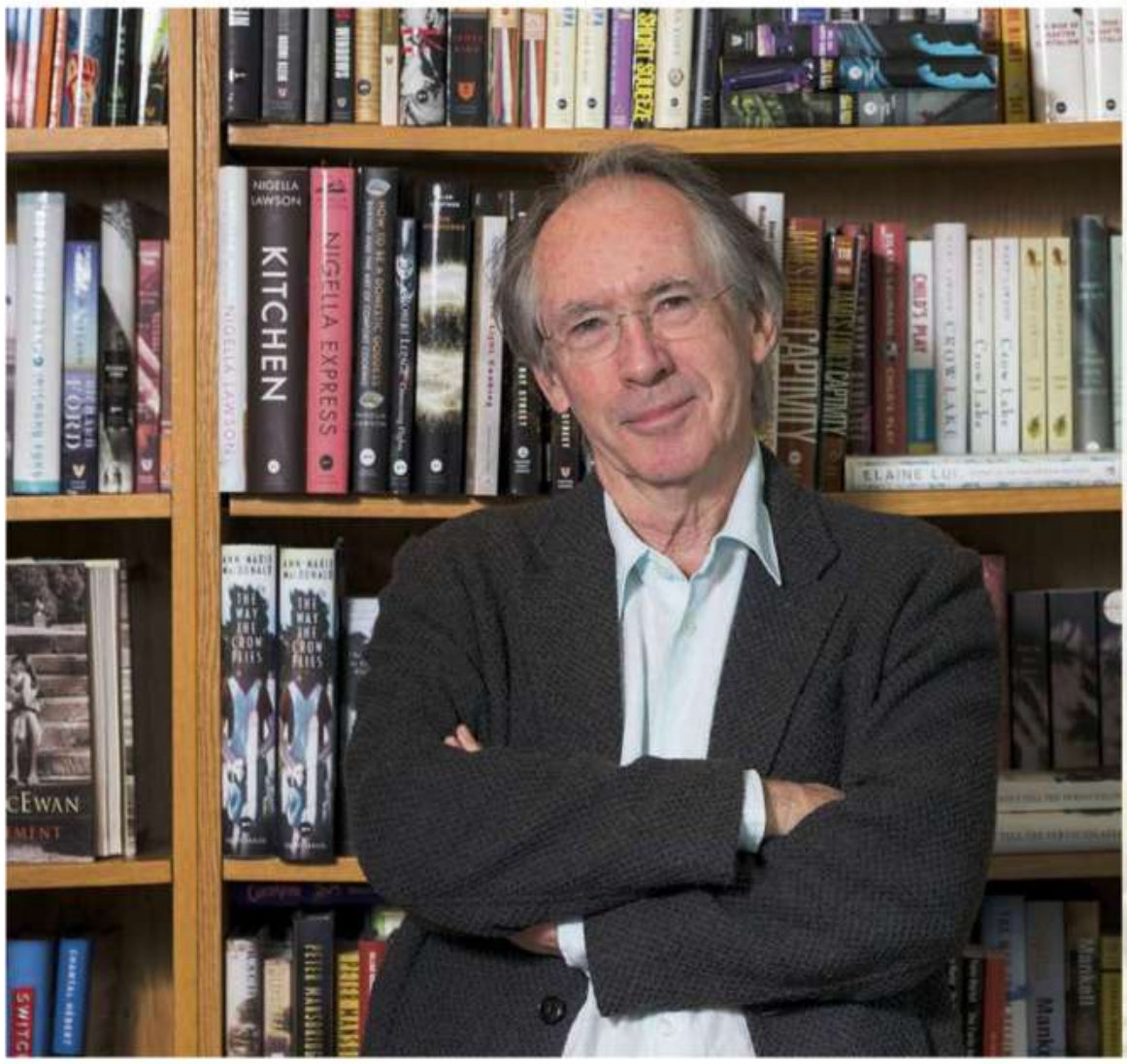


ABOVE Novelist Ian McEwan has vivid recollections of finishing a manuscript for a book he couldn't possibly have written

Dr Rob Nash had been excited to meet the former newsreader Sir Trevor McDonald at his sister's graduation.

"He was getting some kind of honorary degree," Nash recalls. "I was sat right at the back, so all I could see was that he was wearing this awful, garishly multicoloured graduation robe. His speech seemed to go on and on, but afterwards I got the chance to meet him in person."

But Nash, a psychologist at Aston University, Birmingham, discovered a few years later that McDonald hadn't been at that event at all. In fact, Nash realised that even he wasn't at his sister's graduation. He'd invented the whole thing.

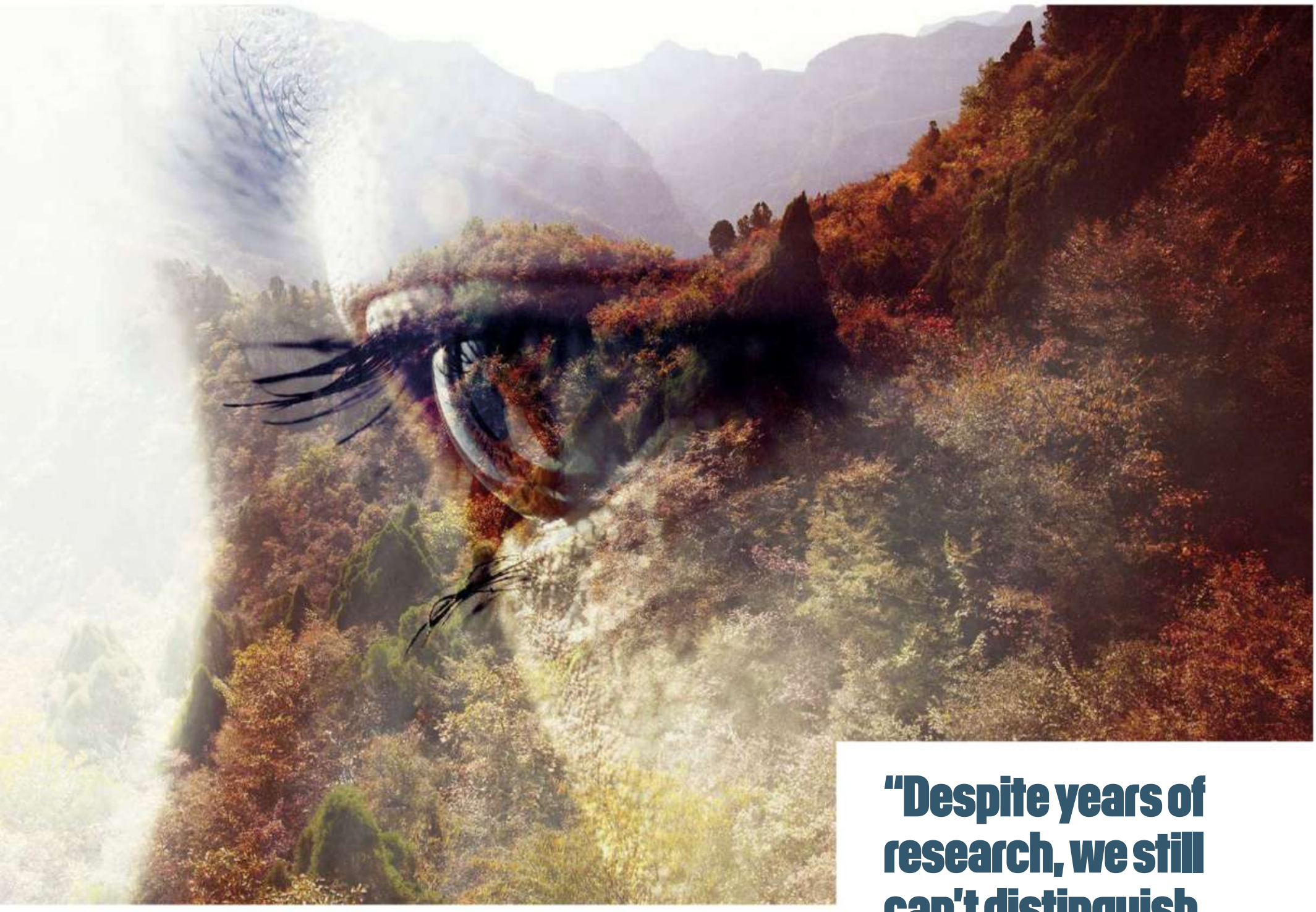
False memories like this are common. Of course, we all misremember things, but false memories can be rich in detail; not so much mistakes as elaborate fantasies. I recall a book of piano pieces that I used to play as a child, a compilation of tunes with the wistful romanticism of Chopin and Fauré. I can still almost remember how some of them went and I'd love to find that book again. But I know I won't, because I've had to gradually accept the truth: I made it up.

In a recent interview in *The Times* newspaper, the novelist Ian McEwan described a similar false memory, of an "incredibly beautiful" novella that he was convinced he'd written and then stowed somewhere. He had since looked everywhere for it.

"I saw it in my mind's eye, the folder, the pages, the drawer it was in," McEwan says. But there was no escaping the truth. "There was no gap in which this work could have been written, my time was fully accounted for. It was quite haunting."

Nash might have expected to be better at spotting his false memory, though – he specialises in studying them. But even his expertise and experience wasn't enough to make him immune.

So why do we get false memories? Over the past decade or so, psychologists like Nash have started to suspect that, far from being a kind of useless mental spasm, false memories might actually have some surprising benefits. It seems that they're able to improve our mental processing: they can help us to think and may be a handy part of our cognitive toolbox.



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REMEMBER, REMEMBER?

Remembering, says Nash, isn't a matter of looking up a fact in a mental filing cabinet. "It's more like telling stories," he says. We forget and invent details. It's hard to know when these don't map onto reality because, as far as we can tell, "memories are our reality". Despite years of research, we still can't distinguish true memories from false ones unless we can independently verify or falsify the remembered facts, which is either impossible or not worth the effort (why should I care if I had porridge last Wednesday, or was it Tuesday?).

What's more, says Prof Mark Howe, a psychologist at City, University of London, "false memories are produced by the same processes as true memories – they are reconstructed from whatever mental imprint remains of the original experience." It's not surprising, then, that it's relatively easy to implant false memories in people by furnishing them with fake evidence. In 2009, Nash and his colleagues filmed subjects performing certain actions and then, days later, showed them the footage after it has been digitally doctored to include some actions they hadn't actually performed. Over half of the participants said they recalled clearly and vividly, carrying out these actions.

In other experiments carried out by Prof Fiona Gabbert and her colleagues at the University of Aberdeen in the early 2000s, pairs of participants were shown footage in which a young woman stole a wallet – but only one of the pair saw it from a perspective in which the theft was actually visible. Yet when the pair subsequently discussed the events between them, around 60 per cent of those who hadn't seen the theft directly swore that they had.

Gabbert also showed people faked CCTV footage of a robbery and had them discuss what they'd seen. One of the participants was a stooge primed to introduce false ideas: the thief had a gun, right? He was wearing a leather jacket, wasn't he? (No and no.) About three in four

"Despite years of research, we still can't distinguish true memories from false ones unless we can independently verify or falsify the remembered facts"

THE DARK SIDE OF FALSE MEMORIES

What if consciously searching for long-buried memories is what drives us to create them?

There's an ongoing debate in psychology about the nature of false memories and their implications for criminal cases. Can false memories be imagined out of thin air, or do they need some kind of 'real-life' seed? And if false memories can materialise out of nothing, what does that mean for the testimonies of defendants, victims and eyewitnesses?

To take one example, in the 1990s, there was a panic that psychotherapy patients were being furnished with false memories of childhood sexual abuse. Could the seeds of false memories of abuse be sown when therapists dig for forgotten childhood traumas to use as explanations of psychological problems, later on in life?

"Although some people can and do have reasonably accurate memories for childhood abuse, there are circumstances under which suggestive interviewing or therapy can create memories of abuse where there are none," says psychologist Prof Mark Howe. In 2015, two psychologists found that interviews with volunteers using repetitive, suggestive questioning led to 70 per cent of them falsely remembering having committed a crime in early adolescence that led to police contact. Their reported memories were rich in detail, despite being demonstrably untrue.

But clinical psychologist Prof Chris Brewin of University College London questions whether reputable therapists work in such a way as to accidentally seed false memories. He also says that false memories are not easily spun out of nothing. "People probably wouldn't be having these memories without a connection to something," he says. Details might be misremembered, but Brewin says there's usually a "grain of truth" in such recollections. The question is whether that grain of truth relates to an actual event or just the memory of a book, TV show or movie, or even something someone once told you.

This aspect of false memory remains highly contentious. Yet Brewin says that clinical specialists agree that recovered memories exist and that "they can be true, false or a mixture of the two." He and psychologist Prof Bernice Andrews argue that, "either uncritically accepting false memories, or disbelieving genuine recovered memories, has the potential to do immense harm."

people later confidently recounted these 'facts' when questioned. This susceptibility – what psychologists call memory conformity – is a big problem for witness testimonies at crime or accident scenes. "The consequences of memory conformity in legal arenas can be far-reaching and serious," says Gabbert. Indeed, false memories have become a legal battlefield in crime cases.

Such contagious suggestibility can lead to mass delusions, as became clear when Nelson Mandela died in 2013 and many people admitted they thought he'd died in prison during the 1980s and could even remember his funeral, a phenomenon now dubbed the Mandela Effect. Rather less somberly, there's the strange case of Walkers crisp packets in the UK. Many people are convinced – wrongly – that the green colour (for salt & vinegar flavour) and the blue colour (for cheese & onion flavour) used to be the other way around.

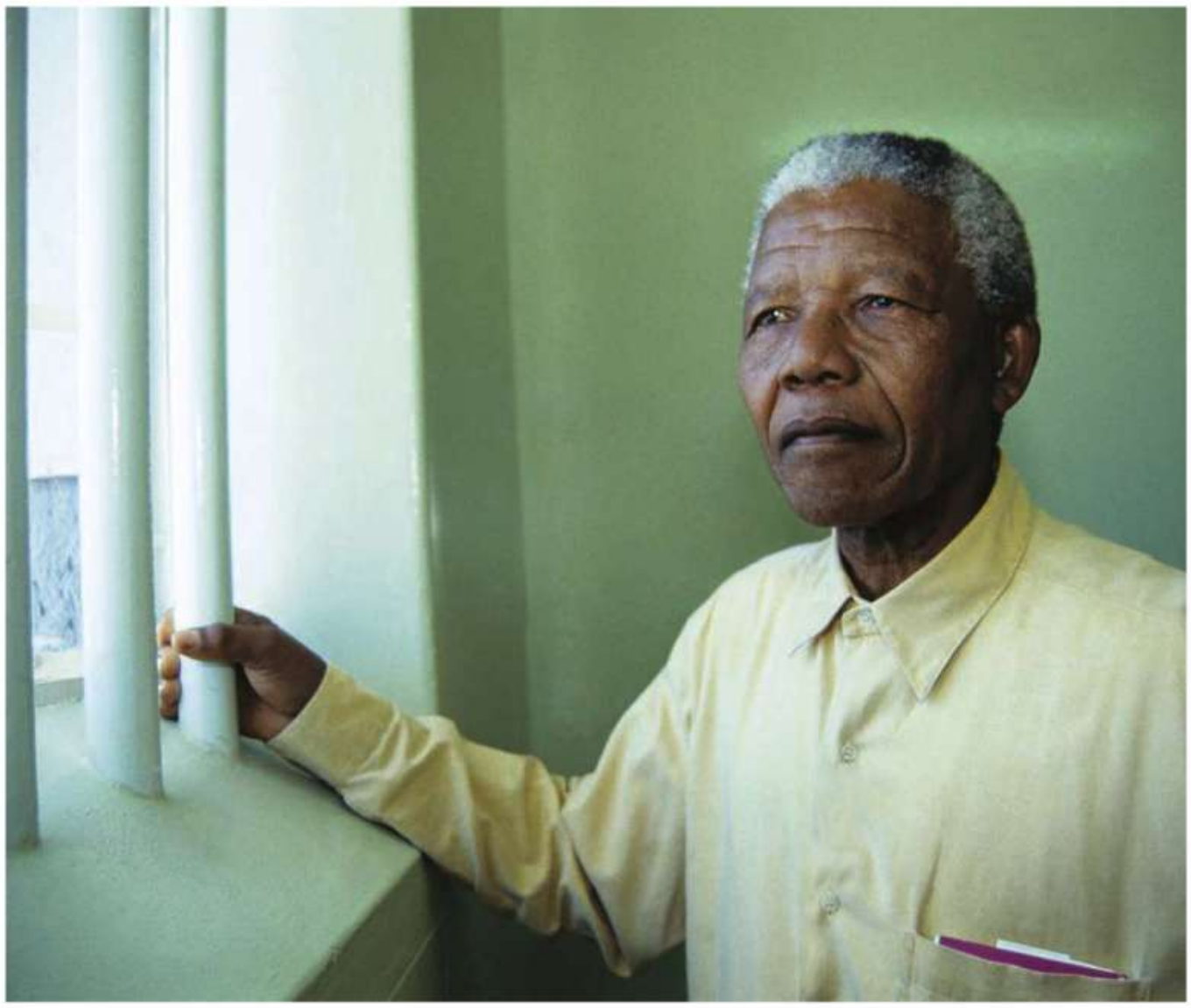
IMAGINED FUTURES

Memory is clearly an evolutionarily adaptive trait: remembering the past helps us prepare for the future. So false memories must be a bad thing, right? If we remember things wrongly, we'll have inaccurate future expectations. It turns out that it's not that simple.

Some cognitive scientists think that cognition works in order to prepare us for imagined future cause and effect scenarios: if I do this, then that will happen as a result. The process relies on gathering and retaining information about how the environment responds to our actions. In this case, sometimes a plausible guess expressed mentally as a false memory of what happened the previous time, is better than having no clue at all. In this way, a false memory can suggest alternative scenarios for decision-making, priming the mind to be better at problem solving. After all, these 'memories' might not be wrong about what would happen in a given situation, but only about our imagined past role in such a case.

Over the years, Howe and his colleagues have demonstrated cognitive benefits of false memories in tests, where participants were presented with words (brush, gum, paste) that were all related to a non-presented word or 'critical lure' (in this case, tooth). When this critical lure was falsely remembered as having been present on the list, performance was actually enhanced on a subsequent problem-solving task where the lure word was the solution. It was as if the mind were saying to itself, "Ah, I know this one because I saw that word on the last list." Howe and his colleagues

"People are convinced the green and blue colours for Walkers salt & vinegar and cheese & onion crisps used to be the other way around"



ABOVE If many people's memories are to be believed, Nelson Mandela died in prison during the 1980s

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also found that false memories could give the same performance boost in tests on lists of words linked by analogy (tooth is to brush, as hair is to wash). The effect works for all ages, from children to older adults.

INACCURATE BUT USEFUL

So false memories can help us to notice associations and connections, and it might not matter if we get the right answer for the wrong reason (in this case, falsely believing that we saw a word on a list). To put it another way, the most useful memory might not be the most accurate one.

Memory illusions might do more than assist factual cognition. For example, they may play a socially adaptive role: we can sometimes unknowingly edit our memories, Howe says, to align with what other people think or feel, helping us feel more connected to them. "Distortions of our past can serve to nurture social relationships by facilitating empathy and intimacy with others," he says. In this vein, Nash says that his father specifically remembered spending time with his grandfather, even though the grandfather had died before Nash's father was born.

In other words, rose-tinted glasses aren't always a bad thing. "If we see our past in a more positive light than we did initially, that gives us a more positive image of ourselves, leading to a greater likelihood of interacting with others and maintaining social relationships," says Howe. And such illusions can increase confidence to good effect: if you remember that you solved a problem easily last time, you're more likely to do that this time, even if the truth is that last time you actually struggled like crazy. For the brain, a false sense of confidence could be a risk worth taking.

The idea that false memories can sometimes have positive value is gaining ground. As Nash's imagined encounter with Trevor McDonald shows, they can be highly inventive, and he suspects that they could be an offshoot of the human aptitude for creativity. "I'm sure that most art and music contains ideas and motifs borrowed and recombined from many other sources," he says. "So one could draw parallels between the construction of memories and of creative ideas."

Initially, Ian McEwan was tempted to find such a creative response to his imaginary novella. "It was perfect in every way," he told *The Times*, adding that if he wanted to recreate that perfection then, "I'll have to write it!"

But for a memory that turns out to be false, that's easier said than done. "By describing it in public and then seeing articles about it," he now tells me somewhat wistfully, "the ghost of this non-existent masterpiece has fled." **SF**

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by **PHILIP BALL** *(@philipcball)*

Philip is a science writer and presenter of Science Stories *on BBC Radio 4.*

ARE MEN FROM MARS AND WOMEN FROM VENUS?

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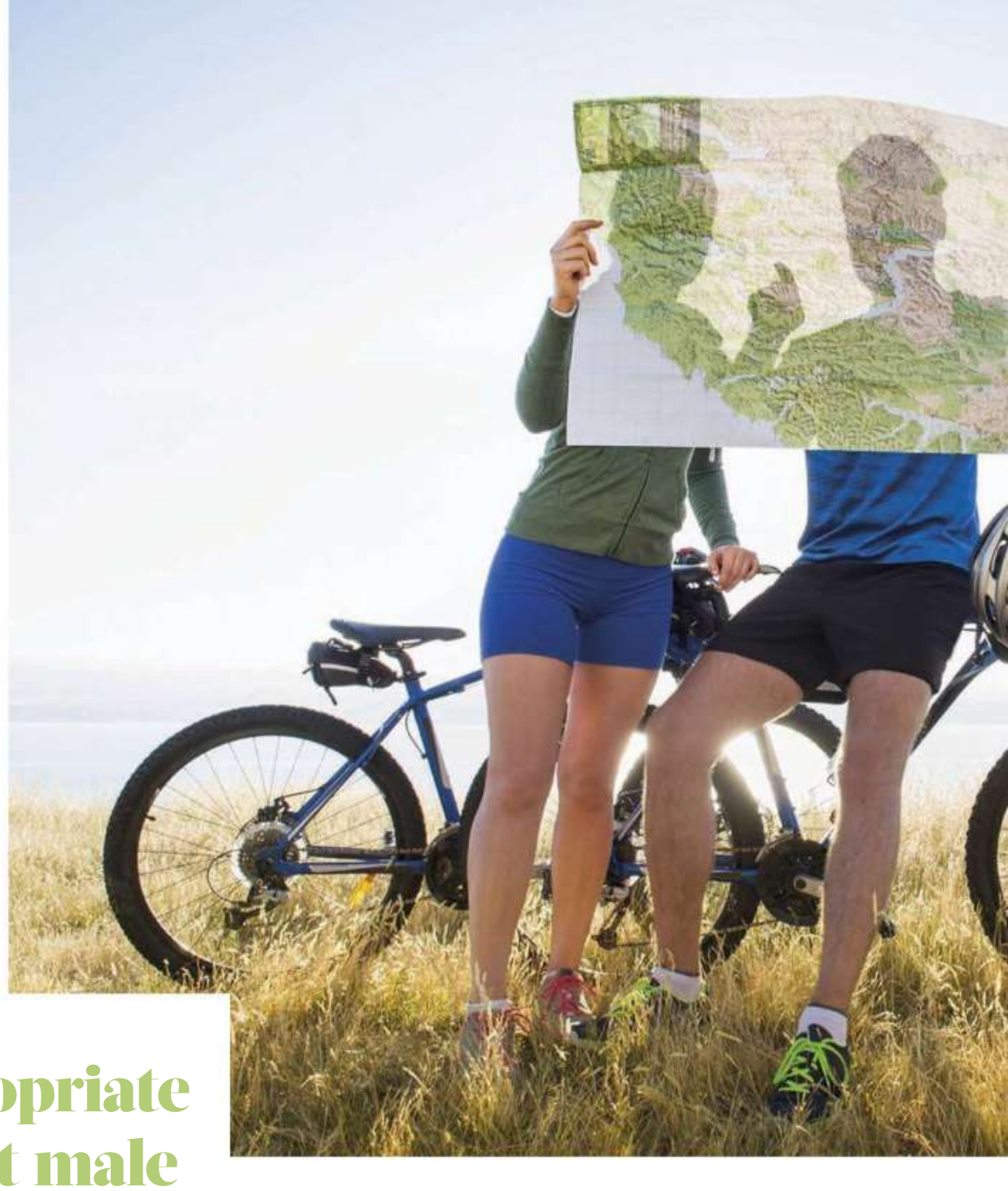
The bestselling book *Men Are From Mars, Women Are From Venus* claims the sexes think completely differently, as if we're from distinct planets. But is this really the case? Do disparities between male and female brains dictate behaviour? And should we stereotype the sexes?

by CHRISTIAN JARRETT



More than ever, people are looking to brain science to answer the perennial question of how men and women differ – and how they might better understand each other.

It's true there are some important differences between men's and women's brains, on average. On this, most experts agree. But contrary to the impression you might get from mainstream media, most of these neurological findings are not relevant – at least not yet – to explaining possible differences in men's and women's behaviour or mental abilities, such as men tending to outperform women on spatial tasks, or women usually showing superior performance on emotional recognition.

Some facts: if you were to hold a typical woman's brain in the palm of one hand, and a typical man's brain in your other, the most obvious thing you would notice is that the man's brain is bigger and heavier. A study from 2005 weighed the brains of 58 women and 42 men at post mortem, and they found that the women's brains averaged 1.27kg, compared with 1.36kg for the men. It's been estimated that this weight difference translates into women having fewer neurons on average in the cerebral cortex by about 16 per cent. Bear in mind that there is a lot of overlap in these statistics, so there are plenty of men who have smaller brains than women.

There are also some average sex-based differences in the size of individual brain structures – for example the amygdala, a brain structure involved in emotional processing, is usually larger in men. The insula, a structure associated with processing internal bodily states, is larger on the left side in men, but larger on the right side in women. Many studies have also reported that the hippocampus, a structure involved in memory, is larger in women. Although, in 2015, a study combining data from previous research on over 6,000 people, concluded that there are no sex-based differences in this part of the brain.

"It is inappropriate to talk about male and female brains in the same binary way that we refer to male and female genitalia"

Another study, also published in 2015, looked at scans of more than 1,400 men's and women's brains. It concluded that most people's brains have a 'mosaic' of structures, some with a more characteristically feminine form and some with a more characteristically masculine form.

"There's not one way to be male or female," says Prof Daphna Joel, who led the study at Tel Aviv University. "There are multiple ways. Most of these are overlapping."

Researchers argued this means that it is inappropriate to talk about male brains and female brains in the same binary way that we refer to male and female genitalia.

BIGGER BUT NOT BETTER

It's important to bear in mind that not only are the findings in this area constantly under revision and debate, but also that the behavioural and psychological implications of any observed sex differences are not always obvious. As a rule, bigger doesn't mean better when it comes to brain volume or individual brain structures.

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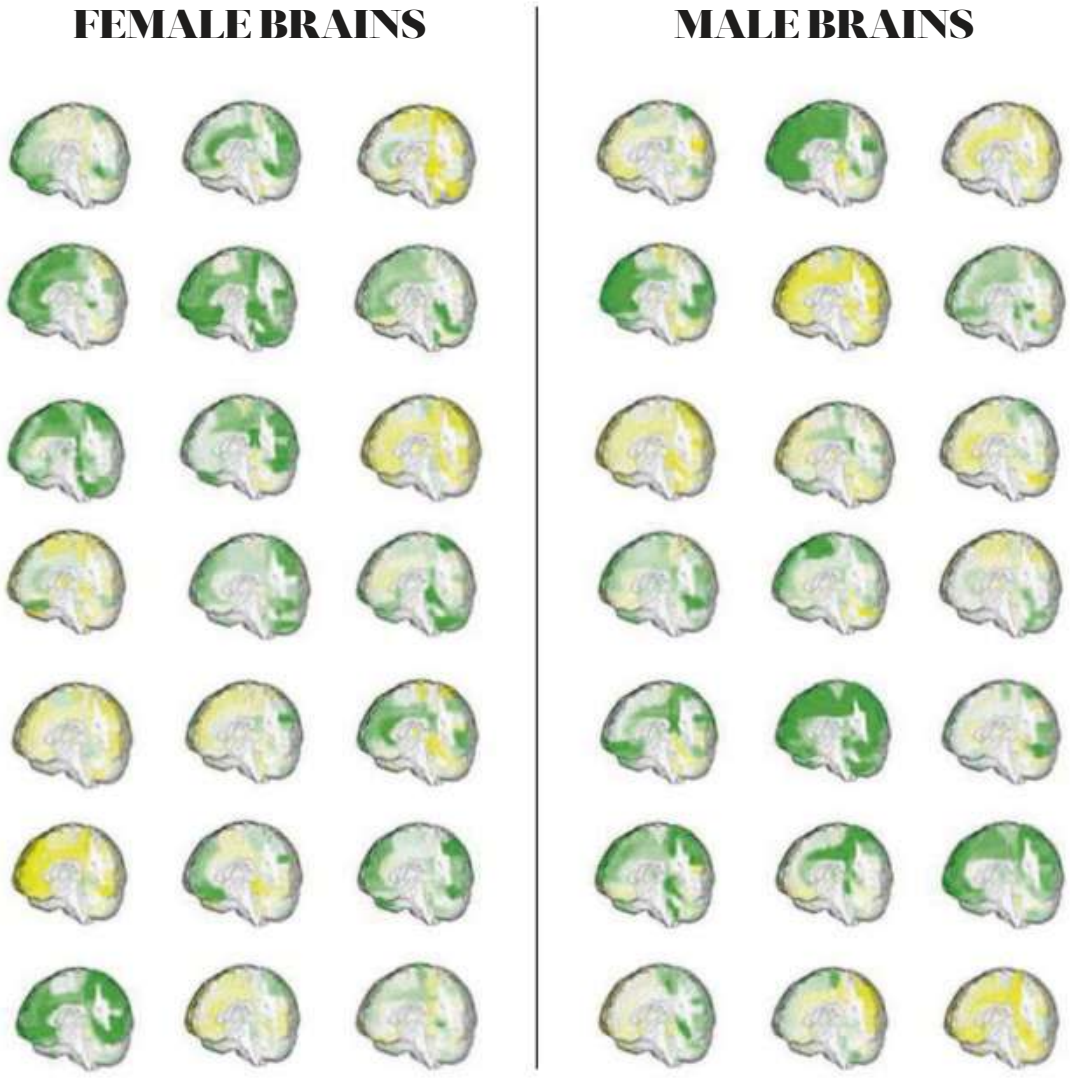
Gender stereotypes suggest that men are better at map reading



To take just one example, expertise in chess is associated with localised brain shrinkage, which is a sign of greater neural efficiency.

Experts like psychologist Prof Cordelia Fine at the University of Melbourne, in Australia, have also argued that many of the average brain-based differences between men and women are more likely to do with the issue of brain size rather than sex *per se*. Smaller brains, whether male or female, are built somewhat differently from bigger brains, and it just so happens that women tend to have smaller brains, on average.

Another theory, proposed by Prof Geert de Vries, of Georgia State University, states that average sex-based brain differences may be compensating for other physiological sex differences, such as in hormones. Viewed this way, sex-linked brain differences contribute to the remarkable behavioural similarities between men and women, rather than their differences.

With these cautions in mind, it's important to recognise that some brain differences between the sexes are important because of their medical implications. For example, women's brains appear more adversely affected by brain injury, and more susceptible to developing Alzheimer's disease and to its effects on cognition. Whereas men seem more inclined to develop Parkinson's, possibly because deep brain structures involved in motor control age more quickly in men than women.

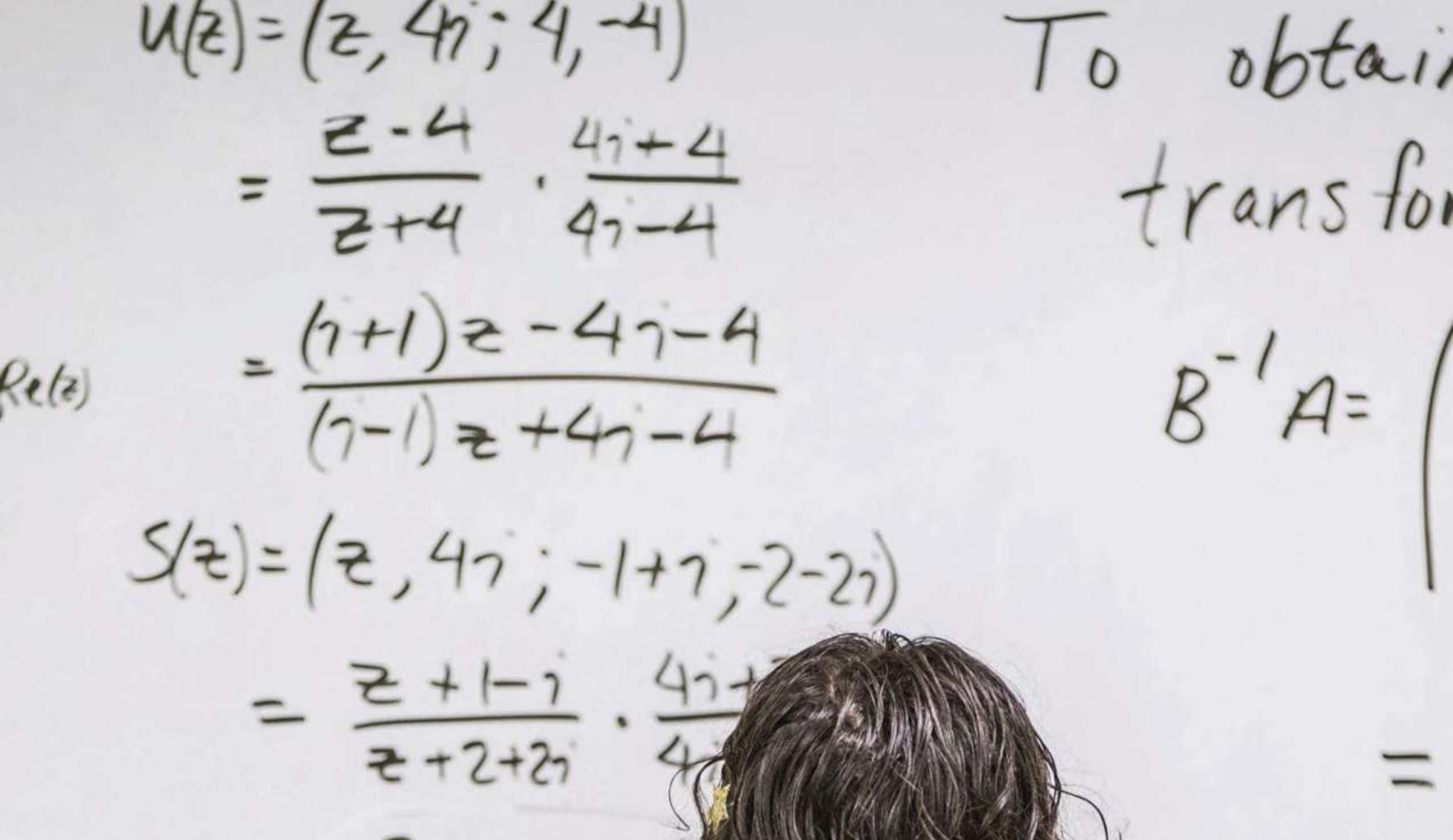
ABOVE Scans from 42 adults, showing brain region volumes (green for large, yellow for small), highlighting features common to both sexes, making it difficult to draw conclusions about differences in male and female brains

Future research into sex-based brain differences could shed light on these issues, as well as the sex differences in vulnerability to psychiatric and neurodevelopment disorders, such as the fact that autism and ADHD are more prevalent in males, while depression and anorexia are more prevalent in females. In this context, some experts such as Prof Larry Cahill at the University of California, Irvine, have raised concerns that so much medical brain research has been based exclusively on male animals, and they've argued that it's critical that female animals are used in testing too.

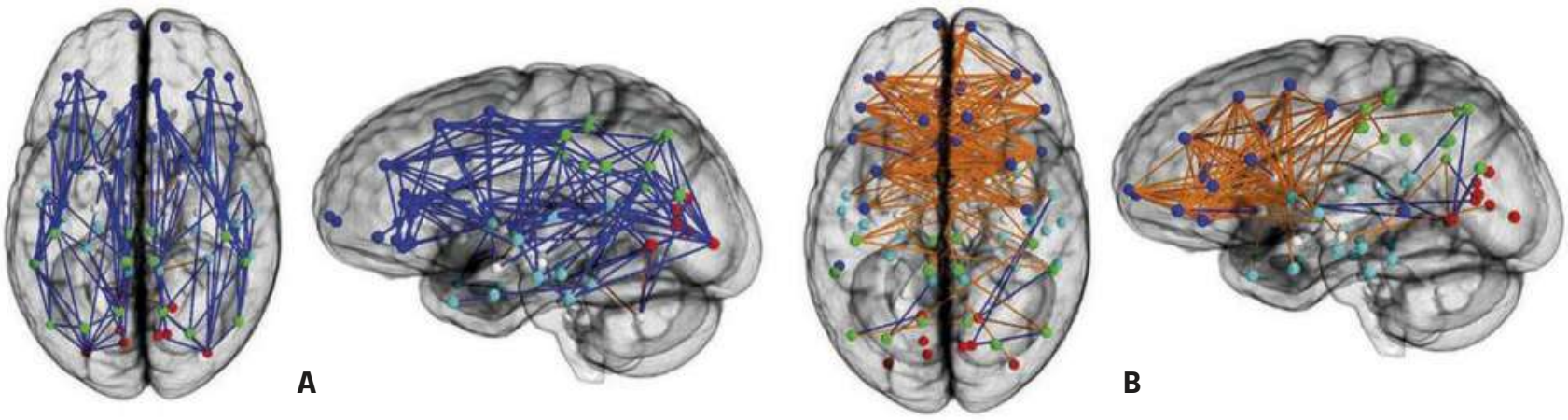
Unfortunately, the medical implications of any sex-linked brain differences tend to attract relatively little news coverage. Instead, there's usually a lot more media interest in any postulated sex-based brain differences that can explain, or even lend credence to, gender stereotypes about behaviour, such as the idea that women are better at being nurturing or that men are better at reading maps.

SEX STEREOTYPING

In 2013, for example, neuroscientists at the University of Pennsylvania plotted the brain wiring patterns of 949 people and said they'd found that, from the age of 14, male brains tended to show more dense connections within each brain hemisphere whereas women's brains showed more connectivity between the ➔



Research shows that women perform better at maths problems when using an alias, possibly because this frees them from the 'stereotype threat'



Connection-wise analysis shows that male brains (A) have more dense connections within each hemisphere, whereas female brains (B) showed more connectivity between hemispheres.

hemispheres. The researchers speculated that this could help explain gender stereotypes, such as that women are better at doing two things at once. The logic was that multi-tasking is made possible by more cross-talk between the brain hemispheres, a mistaken idea re-hashed from John Gray's bestselling book *Men Are From Mars, Women Are From Venus*. Predictably, the media lapped this up, with headlines such as "The connections that mean girls are made for multitasking," which ran in the *Daily Mail*.

It's sensible to treat these claims with some scepticism. The researchers didn't actually measure their participants' mental abilities, such as in multitasking or map reading, so they weren't able to directly link the brain wiring patterns they found with behavioural differences in the sexes. Also, other experts looked at the data and they argued that the brain wiring differences between the sexes were incredibly subtle.

In 2015, the same University of Pennsylvania team followed up with another study in which they measured the connectivity patterns of hundreds more participants' brains, while they lay in a scanner, staring at a cross on a screen. The researchers focused on 264 functional 'nodes,' or hubs (that is, regions in the brain believed to support distinct mental activities), finding that just six (2.3 per cent) showed a sex difference. They also looked at 36,716 specific functional connections in the participants' brains, finding that just 0.51 per cent showed a sex difference. The researchers argued again that these neurological differences might explain sex differences in cognition, but this time they acknowledged: "While sex differences in connectivity exist, on the whole, connectivity patterns of male and female brains are more alike than different."

MYTHBUSTING

One issue when these kinds of brain-based findings filter through to the mainstream media is that they are interpreted by many commentators as providing evidence that any observed psychological differences between the sexes are somehow innate and immutable.

"It fuels unhelpful gender stereotypes that imply men or women are less suited to certain careers because of their brains"

Not only is this logic flawed – any neural difference between the sexes could just as likely reflect a cultural influence as an innate cause – but it also potentially fuels unhelpful gender stereotypes that imply men or women are less suited to certain kinds of careers or pursuits because of their brains.

Indeed, there is research showing that when people are exposed to scientific arguments that say sex differences in behaviour or mental performance are fixed, this increases their belief that any gender inequalities in society are fair and justified. The reality, as shown by many psychology studies, is that gender differences in behaviour are incredibly prone to social influence. For instance, women (but not men) perform better at maths problems when using an alias. Presumably, this is because the alias liberates them from the situational predicament known as a 'stereotype threat' – the fear that their performance will be used by others to support the stereotype that women are not as good at maths as men.

Gender differences in the brain should not be ignored. But neither should they be overstated and used to justify stereotypes. Overall, the research shows that men's brains and women's brains are more alike than different. And as Fine puts it in her book *Delusions Of Gender*: "The male brain is like nothing in the world so much as a female brain." **SF**

by **DR CHRISTIAN JARRETT**
Christian is a neuroscientist and author of Great Myths Of The Brain.

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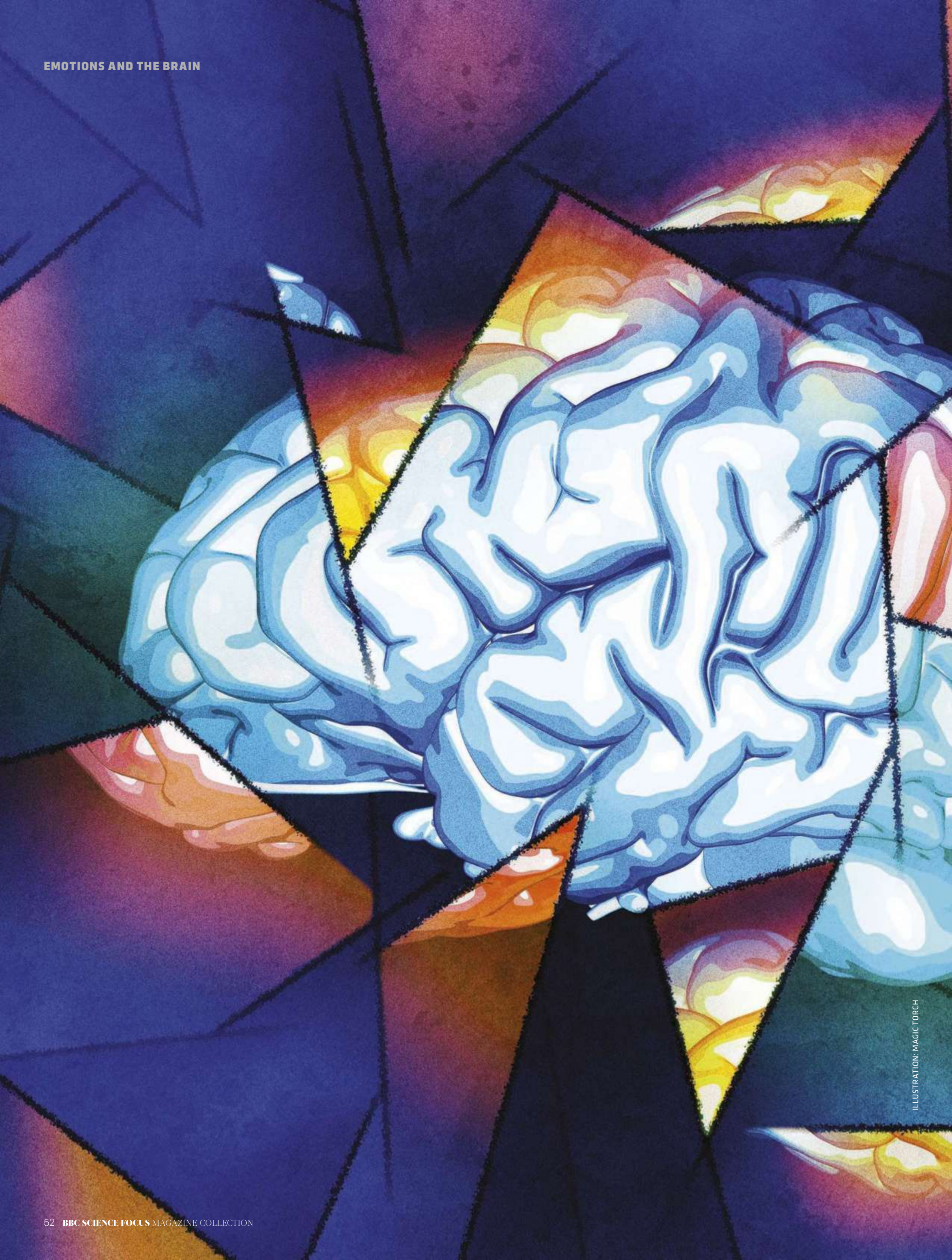

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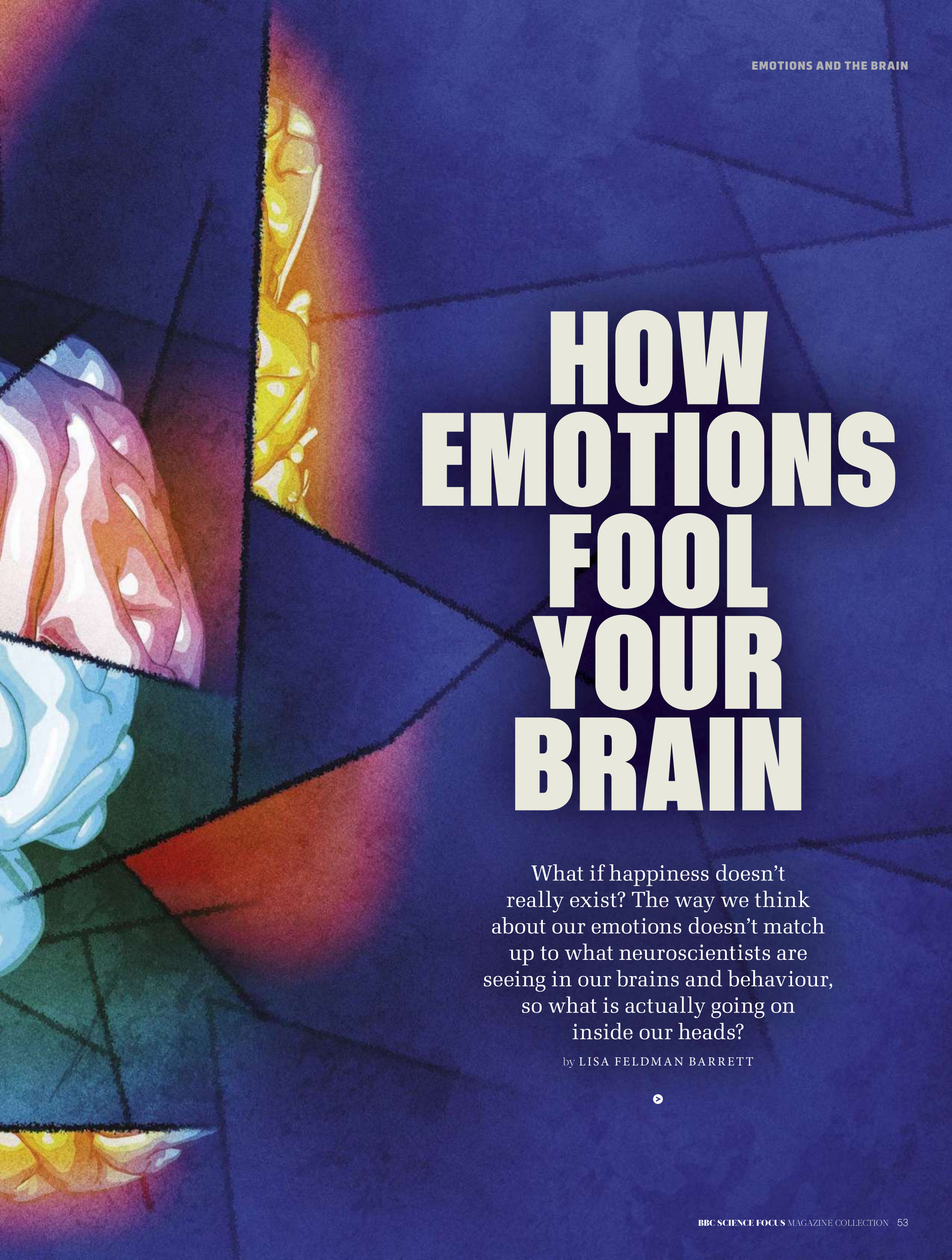


HOW EMOTIONS FOOL YOUR BRAIN

What if happiness doesn't really exist? The way we think about our emotions doesn't match up to what neuroscientists are seeing in our brains and behaviour, so what is actually going on inside our heads?

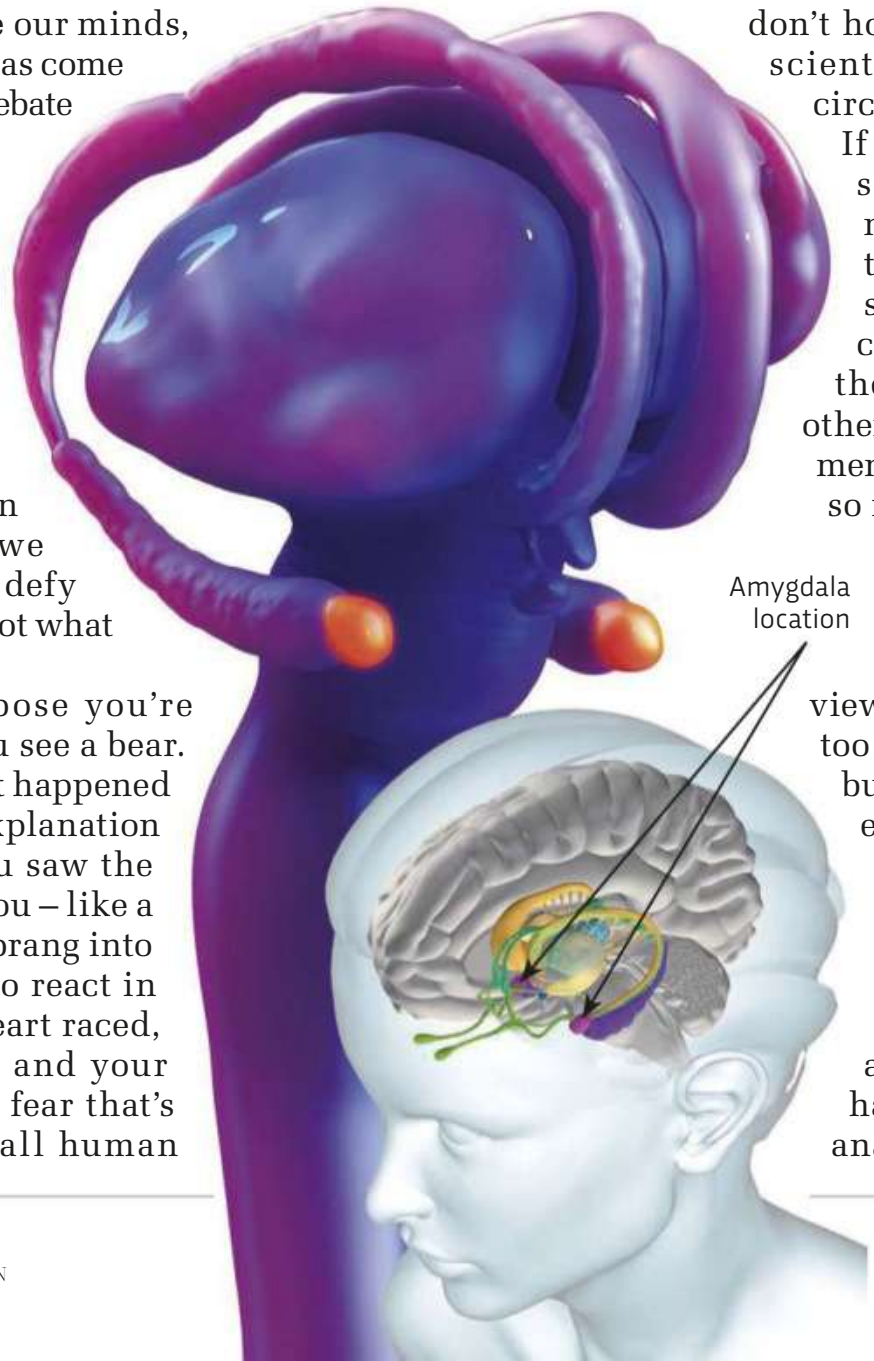
by LISA FELDMAN BARRETT

How do emotions work? This might seem like an odd question since we all experience emotions every day: happiness at seeing an old friend, sadness while watching a tragic film, fear of losing the ones we love. Emotions seem automatic. Your heart skips a beat, your nerves do a little dance, your face moves in familiar ways, and you are carried away by the experience. Nevertheless, from a scientific standpoint, what are emotions really?

For centuries, thinkers like Plato, Aristotle, Darwin and Freud, as well as countless other scientists, have tried to explain emotion using common sense. Emotions feel natural and uncontrollable, the reasoning went, so they must be built into us from birth. In recent years, however, the field of neuroscience, the study of how our brains create our minds, has surged. With this interest has come intense research and renewed debate on the nature of emotions.

A few decades ago, scientists could only guess how the brain creates our emotional experiences. Now, though, we can use brain-imaging to safely peer inside a head. This allows us to observe neural activity, moment by moment, inside living people. And when it comes to emotion, what we see in those brains seems to defy common sense. Emotions are not what most people think they are.

Here's what I mean. Suppose you're walking in the woods and you see a bear. You instantly feel afraid. What happened inside you? The traditional explanation goes like this. As soon as you saw the bear, some dedicated part of you – like a 'fear circuit' in your brain – sprang into action, triggering your body to react in a predetermined way. Your heart raced, your blood pressure soared, and your face formed an expression of fear that's said to be universal across all human cultures. In this classical view of emotion, the firing fear circuit, the bodily changes, and the facial expression supposedly form a distinct, detectable 'fingerprint' that distinguishes fear from all other emotions. That fingerprint was presumably passed down to humans through evolution, along with fingerprints for other emotions.



The amygdala is involved in thinking, memory, empathy and emotion. It is seen here as two orange structures, connected to the hippocampus

GETTY IMAGES X3

CHANGING TIMES

As compelling as the classical view may be, it can't be correct. Scientists have been searching for emotion fingerprints in the face, body and brain for over a century without success. Occasionally, you'll see a news story that scientists have found fingerprints of happiness, sadness, anger, fear, or other emotions in humans or other animals, but when other scientists retest those claims, they invariably don't hold up. For example, for many years, scientists believed that the brain's 'fear circuit' was a region called the amygdala. If you google 'amygdala fear' you can still find thousands of articles that make this claim. Nevertheless, it's not true. We now know definitively that some people who lack an amygdala can still feel fear. Not only that, but the amygdala is involved in dozens of other mental functions (such as thinking, memory, empathy and all other emotions), so it's clearly not a fear circuit. The same is true of every other brain area that has ever been claimed as the home of an emotion.

The main problem with the classical view of emotion is that emotional life has too much variety to be shoehorned into a bunch of universal fingerprints. Do your eyes widen every time you're afraid? Do you always gasp? Of course not. People who feel fear might scream, cry, laugh, close their eyes, clench their fists, wave their arms, strike out, faint, or even stand motionless. We also smile only about 12 per cent of the time when we're happy, according to a recent statistical analysis of many studies, and scowl 28

The Himba people do not associate laughter with an emotion – they simply perceive the person as laughing

per cent of the time when angry. Another study on babies showed that their facial movements are almost indistinguishable in fear and anger. No emotion has a single fingerprint in the body. Variety is the norm.

Not only that, but different cultures have different emotions. For example, the German language contains three distinct angers with different meanings, while Russian has two and Mandarin has five. Plenty of cultures have emotions that don't translate into English. The Ifaluk people of Micronesia, for example, have an emotion called 'fago', meaning love, empathy, pity, sadness or compassion, depending on context. Even more intriguing, some cultures don't have a unified concept of emotion for the events that Westerners experience as emotional. One example comes from the Himba people of Namibia. When you see somebody laughing, you might perceive that they're happy or amused, but the Himba would simply perceive the person is laughing. They don't perceive laughter in mental terms. Throughout the world, the variety of emotional life is too vast to be explained by the classical view.

"Ifaluk people have an emotion called 'fago', that means love, empathy, pity, sadness, or compassion"

HOW ARE EMOTIONS MADE?

The answer to how emotions are made flies in the face of common sense, because the human brain is a master of deception. It creates incredible experiences as diverse as joy, envy, curiosity and wrath without revealing how. But thanks to recent advances in brain imaging, we now have a pretty good idea of the brain's secret technique for making emotion.

Your brain's most important job is keeping your body alive. To accomplish this, it devotes most of its time to predicting what will happen next, so your body can be ready for any contingency. Studies show that your brain spends 60 to 80 per cent of its energy on prediction. In every moment, your brain issues thousands of predictions at a time, based on past experience, and the ones that win are (usually) the ones that fit the situation in the next moment. When you walk, for example, each time you lift your foot to take the next step, your brain anticipates how your foot will land. If your brain gets this wrong, you might trip. If you've ever been in an airport on a moving walkway, and have stumbled as you stepped off (or the last step ➤

just feels weird), you know how prediction error feels. Your brain also makes predictions about other people in the world. Studies show that when you meet strangers, you like and trust them more when their facial movements (such as smiles or scowls) match your brain's guesses. Remarkably, you even consciously see their face more quickly.

Along with predictions about the world, your brain also makes them about your body so you stay alive and healthy. It forecasts when your heart should speed up or slow down, when your blood pressure should rise and fall, when your breathing should deepen, and when you need more salt, sugar, water or hormones, and attempts to meet those needs before they arise. It's like running a budget for your body, but instead of money, the currency is biological.

This budgeting process continues throughout your life, and most of the time, you aren't aware of it. But it produces something you know well: your mood. Somehow, through a mysterious process that nobody understands, physical movements inside your body become mental. You feel pleasant, unpleasant, or anywhere in between. You feel calm or agitated. Your mood is like a barometer for the health of your body. It's with you every moment of your life, though much of the time it's in the background and you don't notice it.

This same process produces your emotions completely outside your awareness. Let's go back to our 'bear in the woods' example. When you're walking in the woods, your brain issues thousands of predictions in every moment, based on past experience. It anticipates each step, the crunch of the dry leaves underfoot, and the look of the greenery above you. It forecasts the heart rate and breathing that you'll need to keep up the pace. Your brain even issues predictions about animals appropriate to the setting, such as bears, and prepares your body to deal with them. It sends signals to your heart to beat faster, your lungs to breathe deeper, and so on, and prepares your body to run. At the same time, your brain guesses how you will feel in a moment from now when you start running and produces an agitated mood. This entire collection of predictions comes from your past experiences of fear. So, if an actual bear shows up in the next moment, you're already starting to run and experiencing fear. That's why fear feels so automatic in that situation, like a reflex. Your brain explains your body's sensations and launches your movements before you're consciously aware.

MORE THAN A FEELING

But what if there's no bear? That's a prediction error, and you'll be left with an agitated feeling with no apparent cause. If you've ever walked in the woods at night and have been suddenly startled for no apparent reason, you've experienced this. There's even a curious third possibility that there's no bear present, but you see a bear anyway, for a moment. You've probably experienced this too. Have you ever seen a person that you thought you knew, but then realised it's a stranger? Same thing. Your brain predicted someone you know, based on past experience, and just for a second, you saw them.

In short, emotions are your brain's best guesses for what your body's sensations mean, based on your situation. When your face feels hot as a driver cuts you off in traffic, you might experience the heat as anger. If you feel the same hot face when you're inches away from having your first kiss, you might experience it as excitement. Or if you feel the same sensation as you walk out of the ocean and realise your swimming costume has fallen down, you might experience it as embarrassment. Your brain makes meaning from the identical sensation in different ways, depending on context. That's how emotions are made. They are not hard-wired

ABOVE If you're in bear territory, your brain is priming your body to react just in case one does show up

GETTY IMAGES, SCIENCE PHOTO LIBRARY

"Your emotions are constructed unconsciously from three ingredients: your body budget, current situation and predictions from past experience"

Brain scans show regions of increased activity, which allows scientists to improve their understanding of emotions. Here, the subjects (male on the left, female on the right) are experiencing jealousy, and the hypothalamus is glowing red

into your brain at birth. Every experience of them is constructed in the moment.

In a sense, your emotions are constructed unconsciously from three ingredients: your body budget, your current situation, and predictions from past experience. If you modify any of these ingredients, you can take some control over your emotions. I'm not saying this is easy, but it's possible.

Changing your body budget is the most straightforward of the three (but again, not easy). Eat healthily, get enough sleep, and exercise regularly, and your brain won't have to work as hard to keep your body budget in balance. That means your mood will be less negative and your brain will have fewer opportunities to create unpleasant emotions.

You can change the second ingredient, your current situation, in a variety of ways. You can directly adjust your surroundings by moving to another location, like leaving the room or taking a walk. If that's not possible, you can indirectly change your surroundings by paying attention to other things around you – or to put it another way, being mindful.

The third ingredient, your predictions from past experience, is the toughest to alter because it's impossible to change your past. Yet if you take action in the present, you can modify your brain's predictions in the future, changing your future emotions. For example, in my family, we came up with an idea we call the 'emotional flu'. Have you ever felt terrible, like you're a horrible person, everybody hates you, and the world is going to end… but in fact, there's nothing actually wrong with your life? That's the emotional flu – you're having an unpleasant physical feeling, probably from a disrupted body budget, and your brain has constructed all sorts of negative explanations that are deeply personal. To deal with these feelings, we took inspiration from the real flu. The influenza virus isn't personal – it simply takes up residence in your lungs. Likewise, we worked hard to view the terribleness as purely physical, and to treat the symptoms with naps, walks, exercise, hugs, or whatever works. By repeatedly reframing the situation from ➲

DICTIONARY CORNER

When you look at the variety of vocabulary used around the world to convey emotions, the traditional concepts of 'happy' and 'sad' start to look a little one-dimensional. Here are 10 of our favourites...

JAYUS
Indonesian / n. / gah-yoose
A joke that is so unfunny (or told so badly) that you just have to laugh.

LEKKER
Dutch / adj. / leh-ker
Tasty (food); relaxed, comfortable; pleasurable; sexy.

GEZELLIG
Dutch / adj. / khe-zell-ikh
Cosy, warm, intimate, enjoyable; often a shared experience (with close others).

NJUTA
Swedish / v. / nyoo-ta
To deeply enjoy, to profoundly appreciate.

AGE-OTORI
Japanese / n. / (archaic) aa-gey oh-toh-ree
To look worse after a haircut; styling one's hair for a coming-of-age ceremony, with the contrary effect of making oneself look worse than before.

BĒI XĪ JIĀO JÍ
Chinese / n. / bay-shee-jeeow-jee
Intermingled feelings of sadness and joy.

FERNWEH
German / n. / fiern-vay
Far/distant pain/woe. The 'call of faraway places'; homesickness for the unknown.

MAMIHLAPINATAPAI
Yaghan / n. / ma-mey-la-pin-ought-ta-pay
A look shared by two people, each wishing that the other would initiate something that they both desire but which neither wants to begin.

SHINRIN-YOKU
Japanese / n. / shee-n ree-n yoh-koo
Taking in the forest atmosphere; forest bathing.

DAGGFRISK
Swedish / n. / adj. / daag-frisk
'Dew fresh'; the kind of pure, clean feeling one might have from waking refreshed in the early morning at sunrise.

↗ The Japanese have a word for forest bathing, shinrin-yoku, which means to take in the forest atmosphere to enhance health, wellness and happiness

DR LISA FELDMAN BARRETT X4, GETTY IMAGES

"Eat healthily, get enough sleep, exercise regularly, and your brain won't have to work as hard to keep your body budget in balance"

personal to physical, my family and I changed our brains' future forecasts, making it easier to create the non-personal, non-judgmental, emotional flu. This was challenging to do at first, but it got easier with practice, and we've passed the idea along to friends who have also succeeded.

I'm not saying you can tweak a few predictions and cure a serious disorder, like anxiety or depression, but it's possible to make tangible improvements in your life. That said, this way of thinking about emotion does have implications for understanding mental illness. For hundreds of years, people have drawn a boundary between mental and physical illness. Cancer, heart disease and diabetes are seen as disorders of the body, while depression and anxiety are often viewed as ailments of the mind. But we now know that your brain constantly regulates your body budget, and when the budget's in the red, you feel bad. This suggests that problems with metabolism, traditionally associated with the body, are at the core of mood-related mental illnesses such as depression and anxiety. It also helps explain why physical illnesses like diabetes and heart disease have persistent mood symptoms. The boundary between the physical and the mental is more porous than previously thought, and understanding this is key to finding new pathways for prevention and treatment.

NEW OUTLOOK

This new view of emotion suggests something important about artificial intelligence. Is it possible to build a machine that can read people's emotions? Companies such as Facebook, Google and Microsoft are betting that the answer is yes. They're spending millions of research dollars to detect emotion via software, by examining faces and bodies as their owners experience emotion. But emotions aren't readable in the face and body alone, because emotions have no fingerprints, and variety is the norm. This means these approaches are asking fundamentally the wrong questions. Tech companies must include more data about a person's context, and embrace the variation in real emotion life.

A tougher question is, can we build a computer that can feel emotion? Our new view of emotion offers an intriguing possibility. If emotion is constructed in part by regulating a body budget, then for a machine to experience emotion, it must have something like a body. Not necessarily a human-like body, but a set of complicated, interacting systems with energy needs that must be kept in balance. No doubt some clever AI developers can figure out a solution. This will bring us closer to creating a machine that can feel and be empathetic. **SF**

by **DR LISA FELDMAN BARRETT**
Lisa is a psychologist and neuroscientist, and author of How Emotions Are Made *(£9.99, Pan Macmillan).*

ABOVE Regular exercise contributes to a good mood, meaning your brain will have fewer opportunities to create unpleasant emotions

↗
Investigating brain development in the womb led Dr Madeline Lancaster to begin growing 'mini-brains'

FELICITY MCCABE

UNLOCKING THE SECRETS OF THE BRAIN

Lab-grown mini-brains could hold the key to solving the biggest mysteries concerning human development and diseases

by KAT ARNEY

Stacks of little plastic dishes in a laboratory incubator, each one holding a blob of human brain, might sound like the stuff of science fiction. But this is no flight of fancy. These blobs, known as brain organoids, are being cultivated in labs all over the world, and researchers believe they could unlock some of the secrets of how our brains grow and what happens when they go wrong.

"I don't think that any of us set out to try and grow a brain in a dish," says Dr Madeline Lancaster, a neurobiologist at the MRC Laboratory of Molecular Biology in Cambridge. "If you'd asked me even just a few months before I started working on it, I would have said it was nuts – but in my case, it was an accident!"

Lancaster's accidental experiments with organoids started when she was a postdoctoral researcher working in Vienna with molecular biologist Dr Jürgen Knoblich, investigating how the brain forms in the womb. She started by ➔

growing brain stem cells in flat layers in a dish, but realised they lacked many of the key characteristics of nerve cells in a real brain. She tried a new technique for growing neural 'rosettes' – flat, flower-like circles of cells that were more realistic, albeit still two-dimensional.

"When I put the cells in the culture dish, there was something wrong with the reagents that I was using," she says. "Rather than forming these nice flat rosettes, mine were forming these weird, floating balls. I thought they looked interesting, so I kept growing them."

Speaking to other researchers in the field, she discovered that some of them had also seen these strange blobs, but had thrown them away because they looked wrong. But while these brain balls looked curious from the outside, what Lancaster found inside was even more fascinating. Each was made from bulging layers of cells connected by cavities, just like the fluid-filled ventricles that connect the hemispheres of the cerebral cortex in a real brain. Even the layers of cells mimicked the arrangement in normal brain tissue, with stem cells lining the ventricles and layers upon layers of more specialised cells and neurons built up towards the outside.

"DESPITE THEIR 'MINI-BRAIN' NICKNAME, THESE ORGANOIDS ARE A LONG WAY FROM BEING FULL-SIZE HUMAN ORGANS"

BUILDING A BRAIN

Despite their 'mini-brain' nickname, organoids are a long way from being full-size human organs. They're around five millimetres in diameter – roughly the shape and size of the eraser on the end of a pencil – and they lack key structures such as blood vessels, which limits how big they can grow. But they are remarkably hardy – they can stay alive for more than a year as long as they're grown in a scrupulously clean environment.

Lancaster's mini-brains are enabling her to prise open the 'black box' of human brain development. Because they reflect the cell types and organisation of a growing human brain, organoids are opening a window into a time of life that has previously been invisible to science.

"People have done MRI scanning on children and even babies to look at how the brain wiring changes, but when it comes to those early events – how neurons are made, how many, which types and where – we can't answer them, no matter how good our MRI machine is," says Lancaster. "But I think what's happening in these dishes reflects what's happening in an actual embryo. We know this because the end product looks a lot like a real brain, so we have a tractable system to start asking some fundamental questions about brain development."

Lancaster is also using her mini-brains to answer an even deeper question: what makes a human brain human? We share more than 95 per cent of our DNA with our closest primate relatives, such as chimpanzees, but our brains are both bigger and different. By comparing brain organoids grown from chimp stem cells with those from humans, she and her team can see how these differences emerge. There's even the possibility of using new genetic engineering techniques to switch human and chimp genes around in mini-brains – something that would be impossible to do in living animals – to pin down the precise molecular pathways that make the human brain so special.

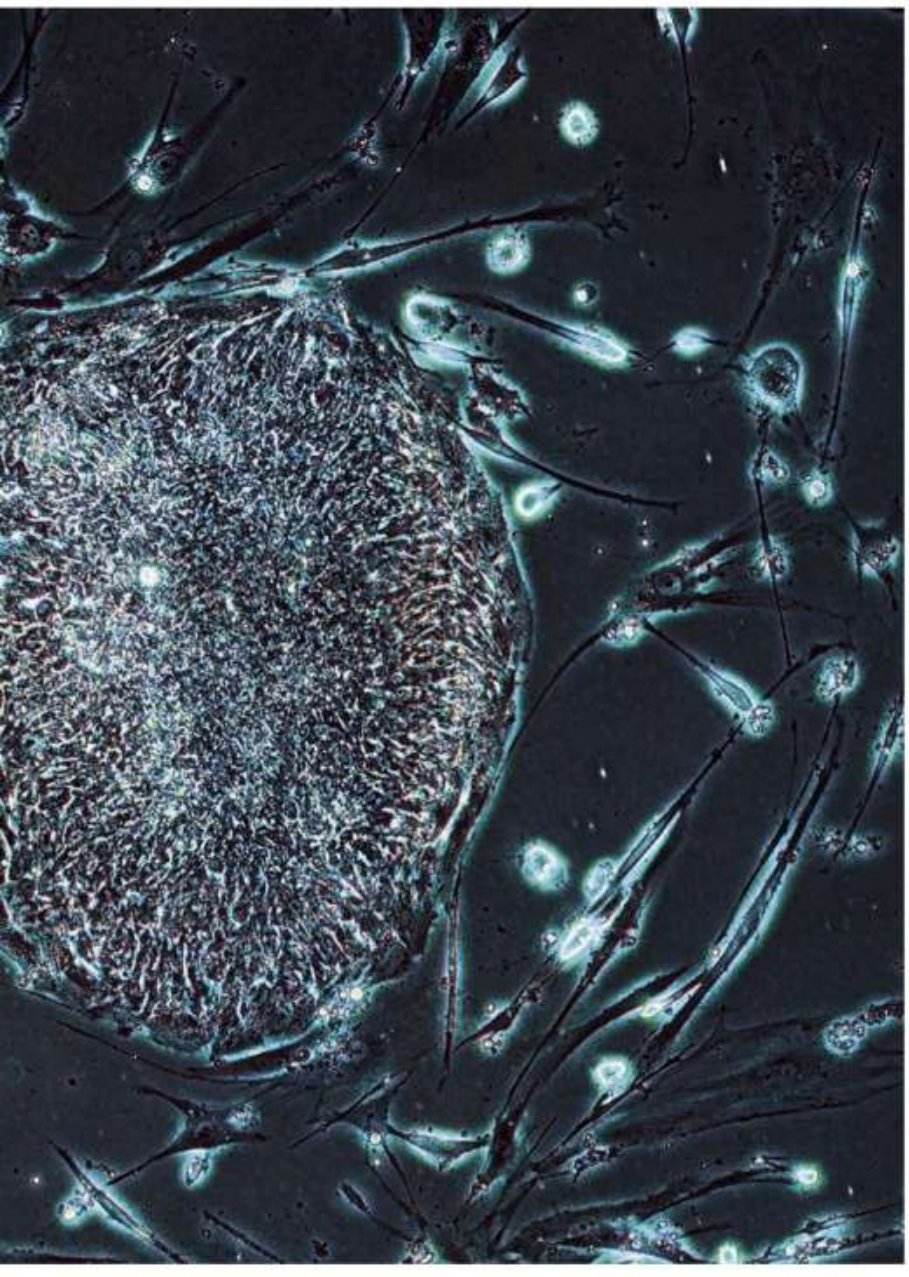
The brain-like appearance of these organoids raises ethical as well as scientific questions. Can they think, and are they conscious? According to Lancaster, the answer is almost certainly no. "I think of them as being a bit like brain tumours," she says. "Tumours contain more neurons than our mini-brains, but no one is concerned that their brain tumour is thinking or has consciousness, and nobody is sad when it has been taken out and thrown away. That's what we have here. It's not an organised network, and it can't make a functional thinking circuit

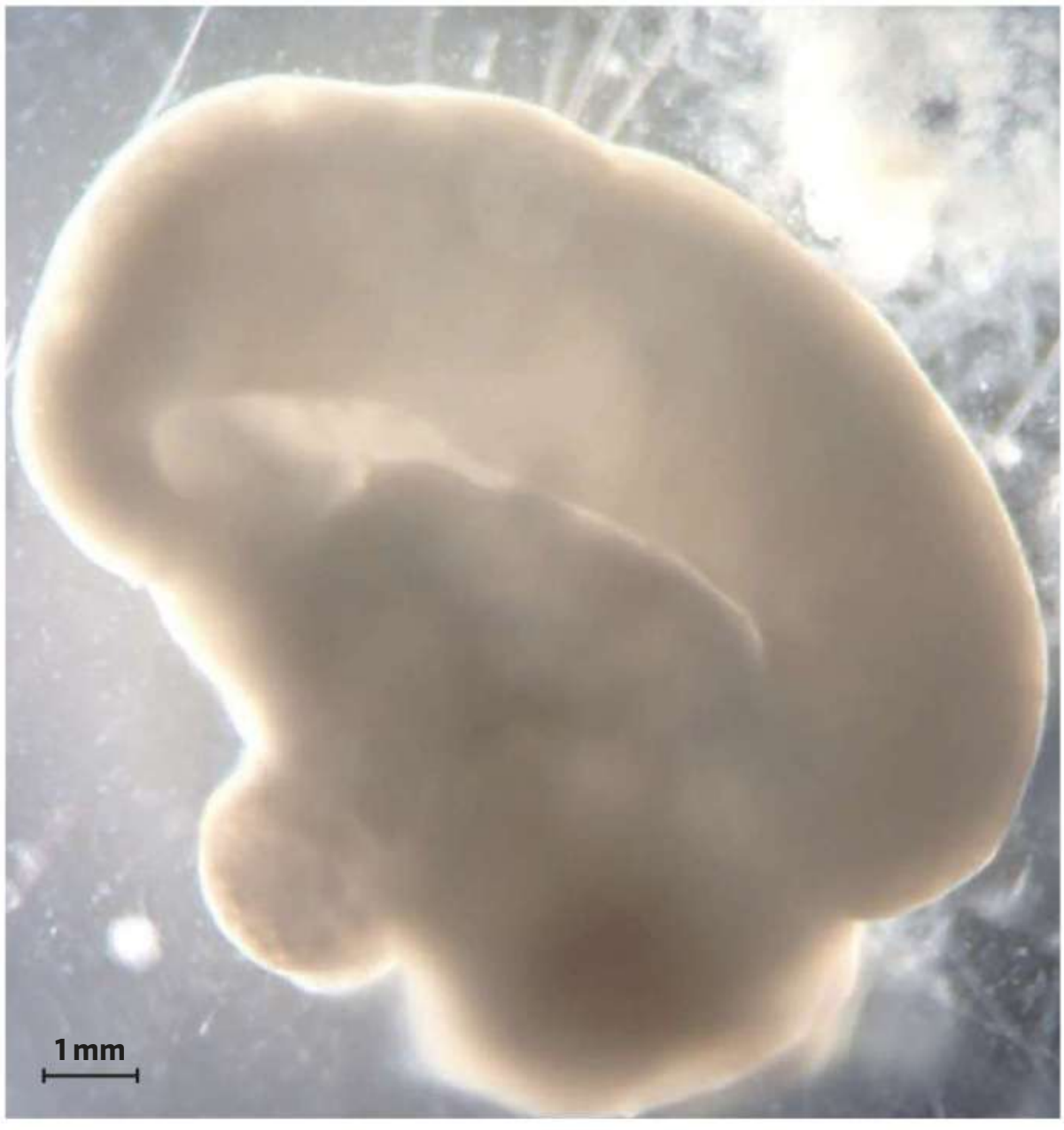
ABOVE The process of building a mini-brain starts with a genetically modified human skin cell

ABOVE RIGHT A bright-field microscopic image of a cerebral organoid. Seen through the naked eye, this mini-brain is just one centimetre across

RIGHT One of Dr Madeline Lancaster's cerebral organoids, seen here in cross-section

MRC-LMB, SCIENCE PHOTO LIBRARY

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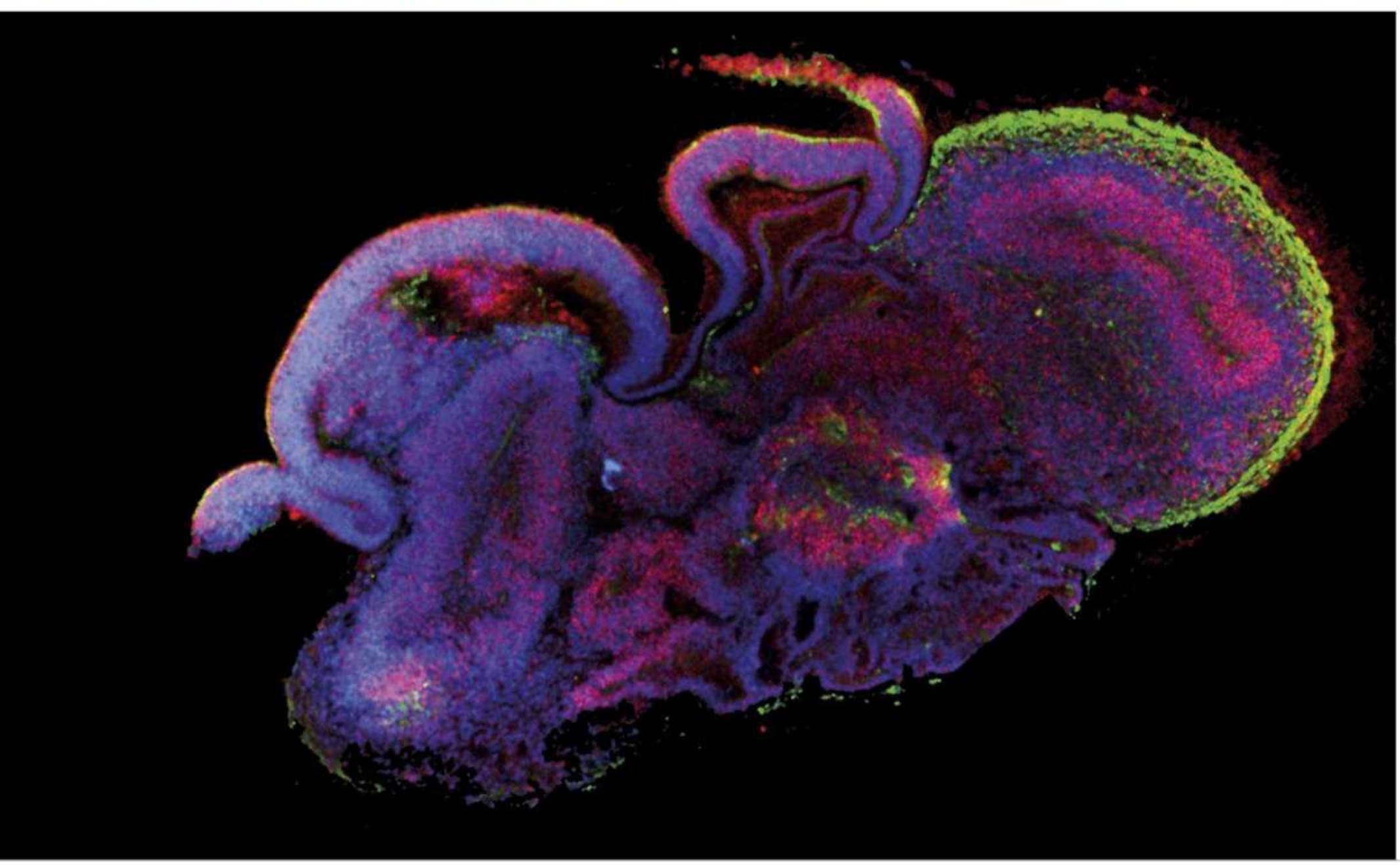


– it's a ball of brain tissue. Just because it has neurons doesn't mean it can think."

Today, she and her team are growing mini-brains from human embryonic stem cell lines – the multi-purpose cells originally found in very early human embryos, but now cultivated in the lab. She's also using so-called induced pluripotent stem (iPS) cells: adult cells that have been pushed back to an embryonic state using a cocktail of molecules. Depending on the exact conditions used, Lancaster can nudge her organoids to develop all kinds of cells, from the fluffy choroid plexus (which would connect with blood vessels in a real brain) to pigmented light-sensing cells that are usually found in the retina at the back of the eye.

"There's just so many cell types to look for," she says, "But depending on the method we use, every time we look for something that we know should be there, we find it."

WIRING UP

Mini-brains don't just let researchers study normal developmental processes. Dr Sergiu Pasca, at Stanford University in California, is using them to understand what causes autism, schizophrenia, epilepsy and other neuropsychiatric disorders.

"Most of the psychiatric drugs we have today were discovered by chance – we know very little about the origins of the disorders [they're used to treat] and the question is why?" he asks. "Unlike cancer biologists, who can remove a tumour, put it in a dish and find ways to treat it, we can't do that with the brains of our patients with mental disorders."

Pasca and his team have managed to grow mini-brains for more than two years – a staggering 800 days is their current record – and have shown that they can generate most of the cell types and structures found in real human brains. They're using the technique to investigate the roots of autism and epilepsy by generating organoids with iPS cells derived from skin samples of affected children and then comparing them with cultures grown from healthy cells.

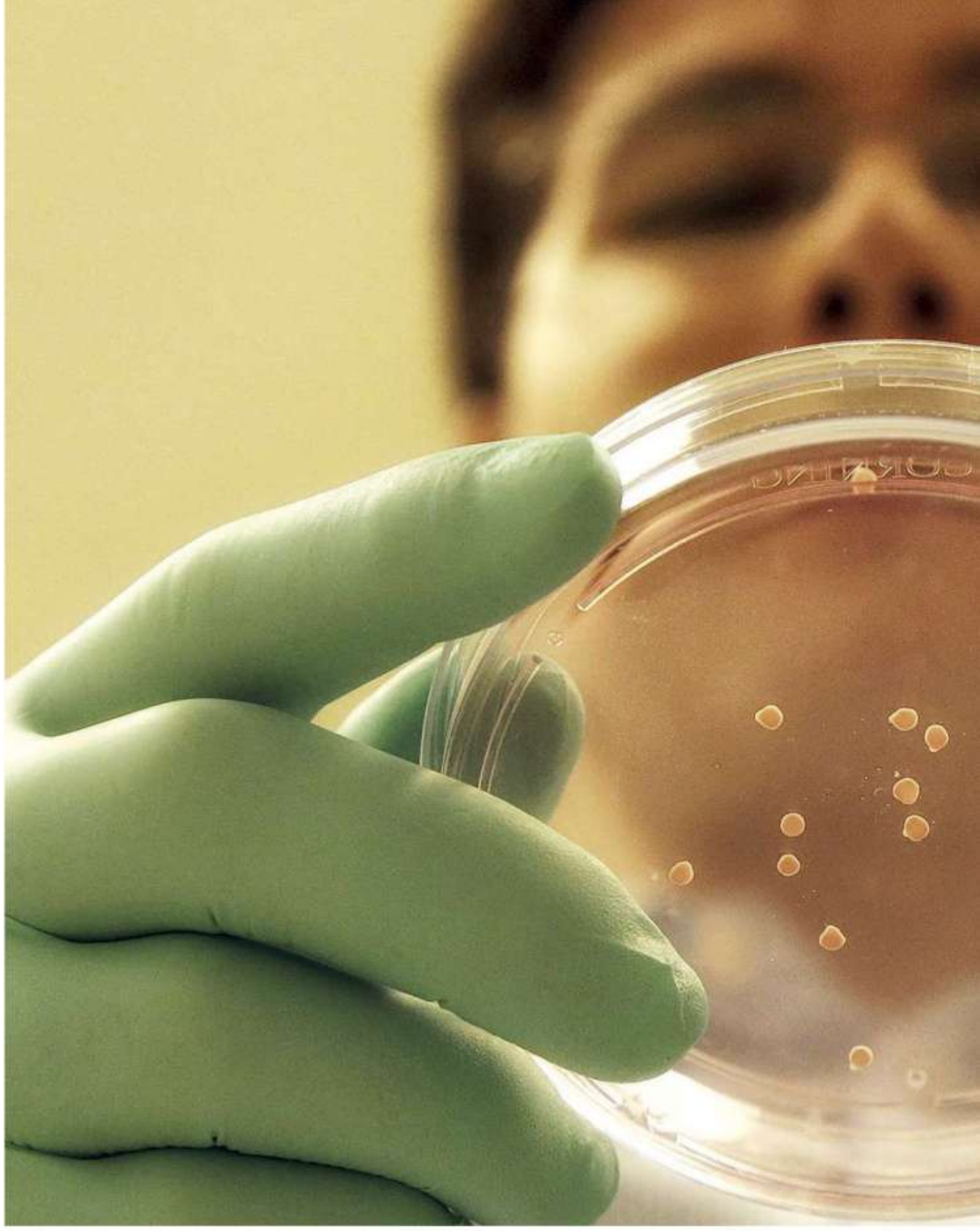
"We can use electrodes to measure how the cells are talking to each other, and microscopy to see how the cells move and make connections," he explains. "Many of the genes associated with these disorders are involved in the connections between nerve cells, so we can see how the gene changes in these patients are impairing the communication within the brain in a non-invasive way."

He's now taking these ideas even further by combining organoids to mimic different regions of the brain and studying their interactions – a technique he describes as "brain Lego". The team is using these hybrids to spy on the brain as it wires itself up, focusing on what happens to so-called inhibitory neurons that normally help to calm down brain activity but are faulty in people with epilepsy and autism.

"Inhibitory neurons are not born in the cortex on the surface of the brain: they are born in a very deep region of the forebrain and have to migrate millimetres over many months after birth," Pasca says. "It's really fascinating to watch in our cultures – they kind of pull themselves up and jump along."

But when Pasca and his colleagues looked at organoids grown using cells from patients with a form of autism that is associated with epilepsy, they saw a different picture. The inhibitory cells were moving in a peculiar way, jumping more often but less efficiently and eventually getting left behind.

Impressively, the researchers were then able to identify a particular drug that could rescue these lagging cells, correcting the wiring defect and pointing towards a potential future



ABOVE Dr Sergiu Pasca holding the mini-brains he's using to study the development of conditions such as autism

RIGHT Dr Selina Wray, of University College London, is using mini-brains to research Alzheimer's

SHUTTERSTOCK

“I WANT TO BUILD MODELS IN THE LAB THAT WILL LET US LOOK AT THE VERY BEGINNING OF DISEASES LIKE ALZHEIMER’S AND DEMENTIA”

treatment for children who are suffering from the same condition.

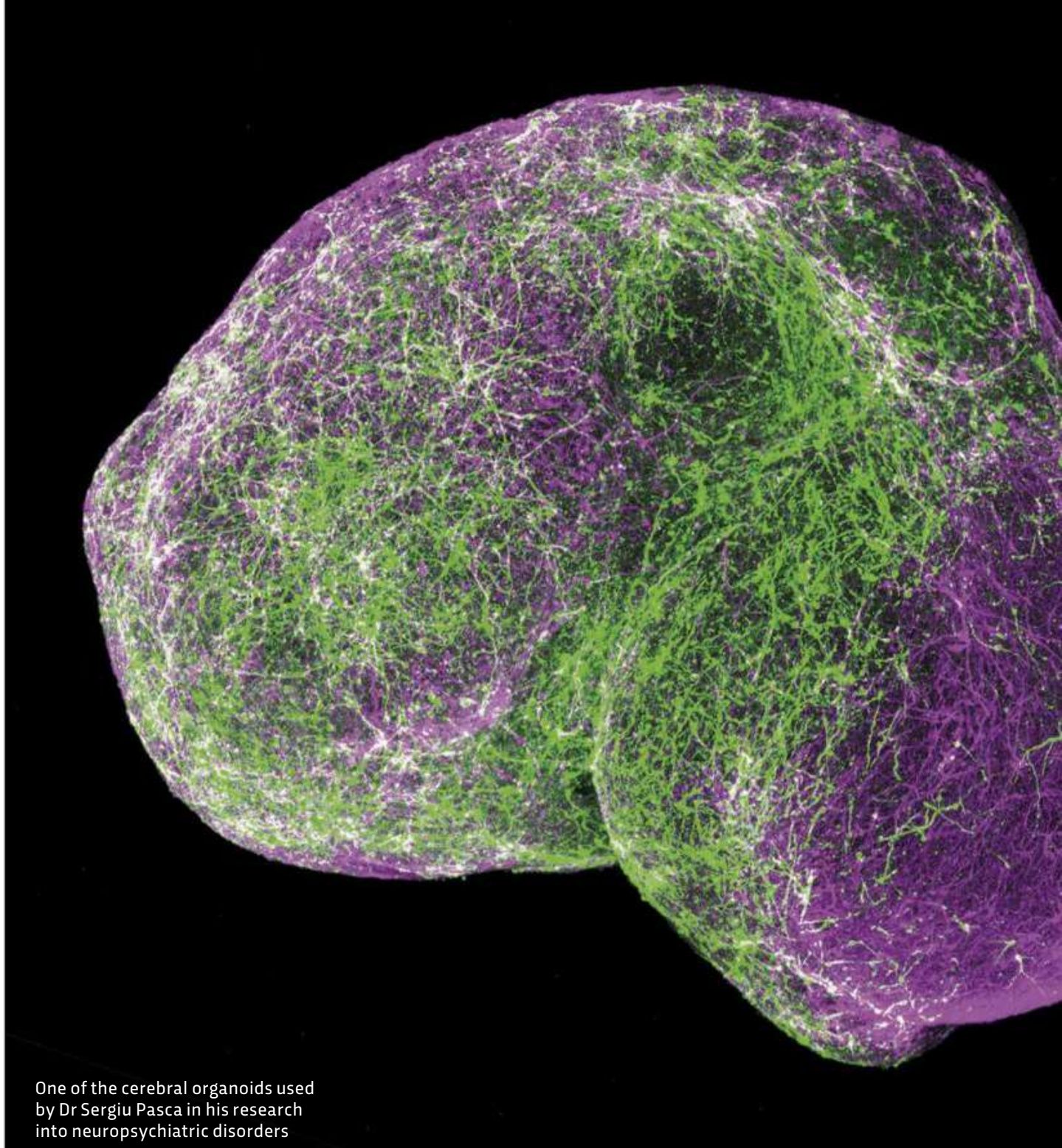
INTO OLD AGE

Meanwhile at University College London, neurologist Dr Selina Wray is using brain organoids to look at neurodegenerative conditions that start at the other end of life, including Alzheimer’s disease and fronto-temporal dementia.

“Normally we have to work with post-mortem brain tissue from patients, but you’re only ever looking at the end stages,” she says. “It’s almost like coming to the scene of a crime after the criminal is gone, and you’re trying to piece together a sequence of events by looking at the damage that’s been left. I want to build models in the lab that will let us look at the very beginning of the disease – because if we understand the first things to go wrong, treatment should be more effective.”

In a similar way to Pasca and Lancaster, she’s taking samples of skin from patients with dementia, turning them into iPS cells and then growing organoids. Wray can spot differences compared with organoids from unaffected people after just a few months, ➲

"MINI-BRAINS MIMIC THE VERY EARLIEST STAGES OF LIFE, WHILE DEMENTIA IS A PROBLEM THAT TAKES DECADES TO DEVELOP"



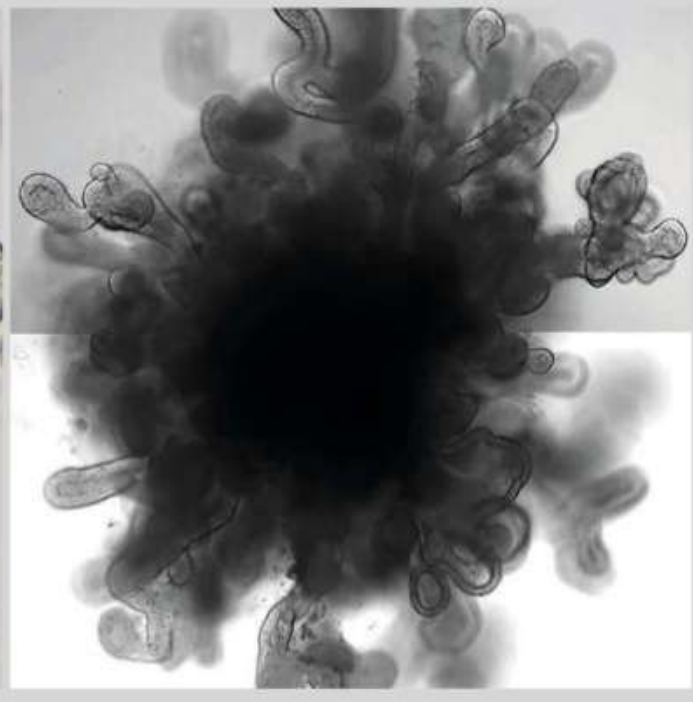
One of the cerebral organoids used by Dr Sergiu Pasca in his research into neuropsychiatric disorders

ALL THE ORGANOIDS

It's not just brains: researchers are creating organoids from many different types of tissue, not only to study healthy development but also to discover what happens when things go wrong in order to develop future therapies. Here are some of the types they've managed to grow so far...

GUT

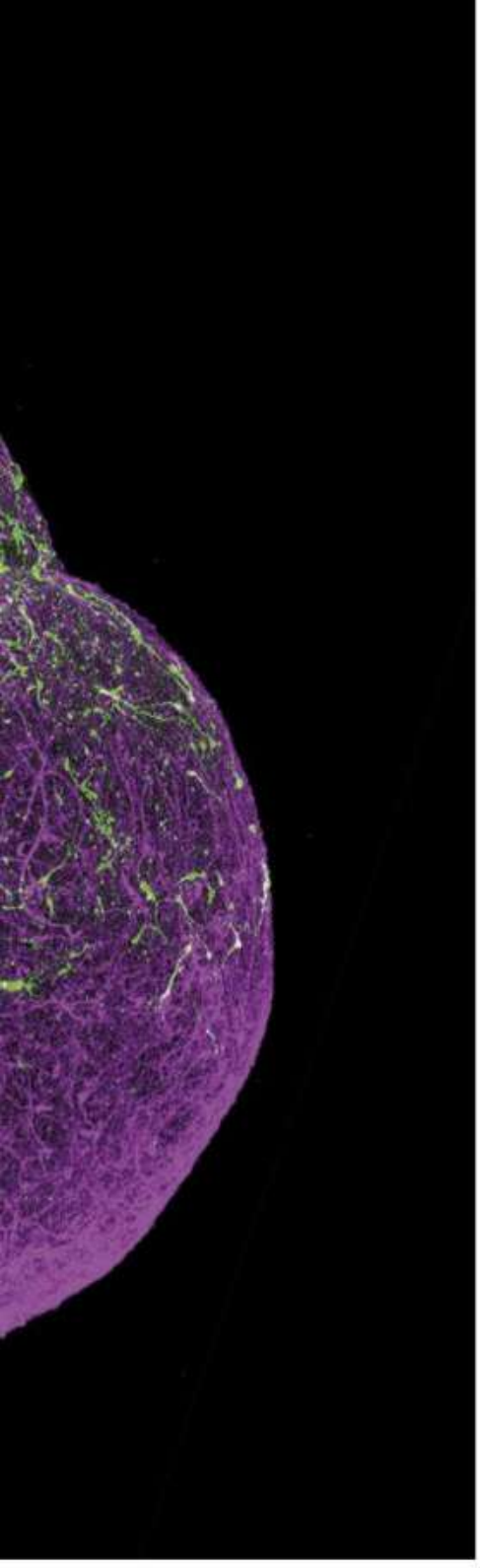
Scientists have made organoid versions of many parts of the gastrointestinal tract, from tastebuds to the intestines. Intestinal organoids can be manipulated to produce insulin, suggesting possible future treatments for diabetes.



LUNG

Although they're a long way from a 'lung in the lab', lung organoids grown using reprogrammed stem cells from patients with diseases such as chronic asthma and cystic fibrosis could be useful models for finding new treatments.

UCLA, SCIENCE PHOTO LIBRARY, CHARLIE ARBER & CHRIS LOVEJOY/UCL

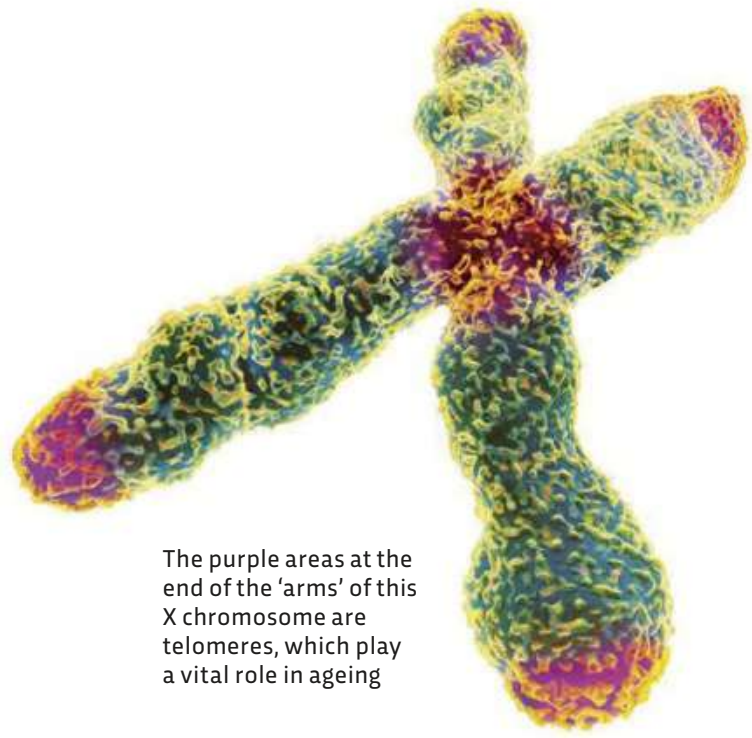


finding increased levels of the forms of certain molecules that are associated with Alzheimer's disease.

But there's a problem with this approach: mini-brains mimic the very earliest stages of life, while dementia is a problem that takes decades to develop. To solve this, researchers are working on ways to speed up the ageing process of the mini-brains. One idea is to add in genetic changes that mimic progeria – a rare disorder that causes dramatic premature ageing. Another approach is to meddle with the structures protecting the ends of DNA inside cells, known as telomeres, which act as a kind of countdown clock as we age.

As well as studying the underlying processes that drive dementia, Wray believes that mini-brains have a lot of potential for helping to identify the correct treatment for individual patients.

"I'm excited by the idea of personalised medicine – that you could take somebody's cells and grow organoids in the lab, screen a panel of drugs against them and say, 'Okay, we think this person will respond to drugs ABC, but that person will respond better to drugs XYZ,'" she says. "That's happening in cancer biology, this idea of being able to stratify patients on a molecular basis, and while I think we are a long way off, I love the idea of growing someone's neurons so we can work out what therapies we should be giving them."



The purple areas at the end of the 'arms' of this X chromosome are telomeres, which play a vital role in ageing

Pasca is similarly enthusiastic about the potential of mini-brains to change lives. "Our organoids are grown from cells taken from real patients," he says. "These kids have severe neurodevelopmental disorders that really impair their lives, and to think that a few months later you can derive brain tissue from those patients in a dish and start asking questions about how the disease may arise – that's what makes this exciting." **SF**

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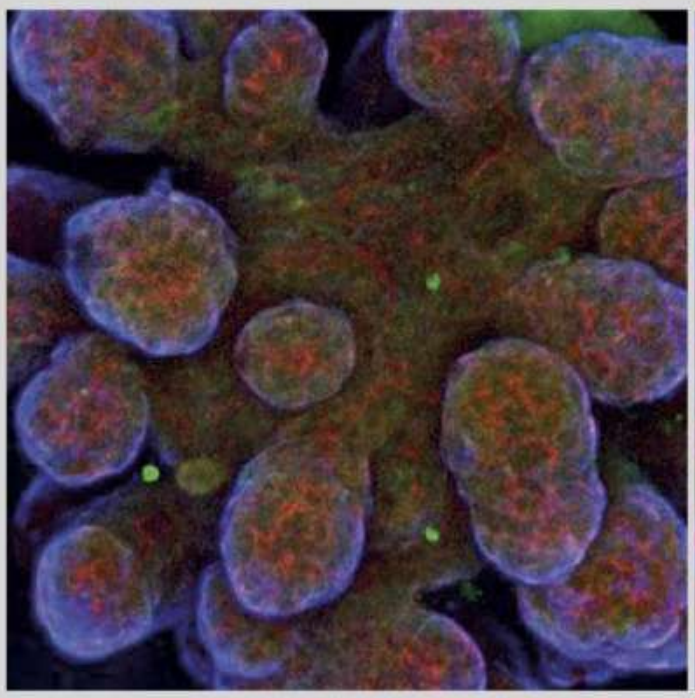
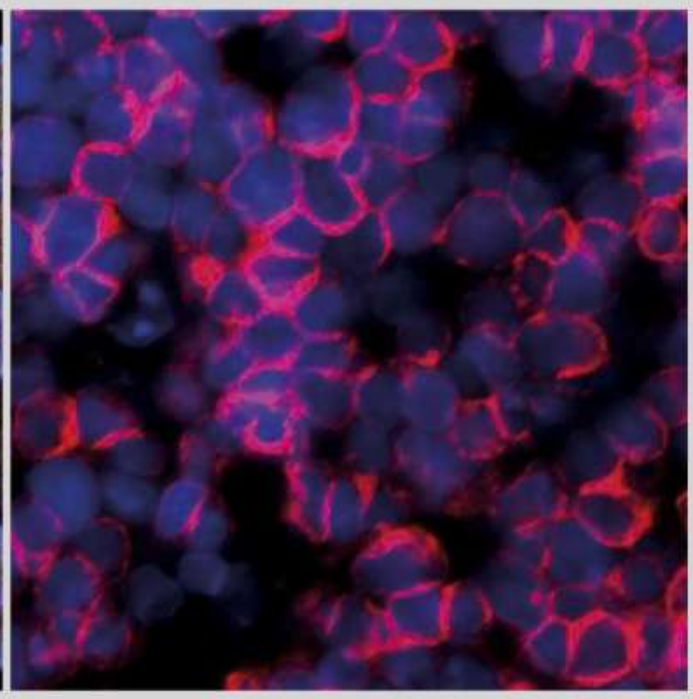
by **DR KAT ARNEY** *(@Kat_Arney)*
Kat is a science communicator. Her latest book is The Compact Guide: DNA *(£8.99, Andre Deutsch).*



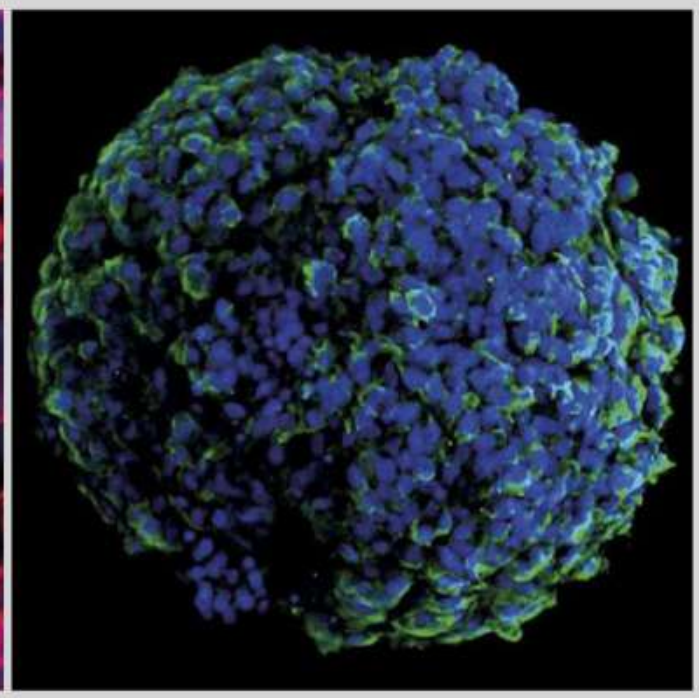
BREAST

Mammary organoids develop the same branching structures that are found in human milk ducts. Because many breast cancers start from such ducts, these organoids are providing vital insights into the growth of breast tumours.



THYMUS

The thymus gland is the place where infection-fighting immune T-cells mature. Thymus organoids can produce functional human T-cells, which could potentially be used to restore the immune system in transplant patients.



HEART

Cardiac organoids are revealing hidden regenerative pathways that could be reactivated to treat heart disease. Researchers also created organoids with functional, beating chambers, as a model for studying heart failure.


CAUTION
SECRETIV.
ACQUISITIV.
CONSTRUCTIV.
DESTRUCTIV.
COMBATIV.
ALIMENT.
VITATIV.
CONSCIEN.
HOPE
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VENERATION
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MIRTH
TUNE
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ORDER
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THE SCIENCE OF SANITY

Over the last century, almost 250 new psychiatric conditions have been identified, from attention deficit disorder to hoarding disorder. Here, we investigate the fine line between what is considered sane and insane

by JO CARLOWE

They say there's no clear boundary between sanity and madness. But in 2013 the distinction between them became more obscure, thanks to the publication of the fifth edition of *The Diagnostic And Statistical Manual Of Mental Disorders* (DSM-5). It is produced by the American Psychiatric Association (APA) and is a 'bible' for many people in the healthcare world.

DSM-5 generated a storm of controversy when it was released. Critics argued that it classified what should be considered ordinary behaviour as madness, with the British Psychological Society warning that normal experiences would be given "potentially stigmatising medical labels" and result in "potentially harmful interventions."

First published in 1952, the DSM is a practical guide for psychiatrists, with a check-box of symptoms for all recognised mental health conditions. The idea is that psychiatrists match their patients' complaints against them to find an appropriate label for their condition: bipolar, acute stress disorder, somatic symptom disorder (hypochondria), and so on.

The new edition was the first time the APA had fully updated the DSM in nearly two decades. The furore was caused by the

GETTY IMAGES

15 new mental disorders included in the new edition. Becoming overwhelmed with grief when a loved one dies was now diagnosed as 'major depressive disorder'. Getting horribly nervous before a speech might mean you have 'performance-only social anxiety disorder'. Even failing to throw out old junk could have you labelled with a 'hoarding disorder'.

GOOD GRIEF

It was the removal of 'the bereavement exclusion' that caused the most concern. This advised doctors to refrain from diagnosing major depression in individuals within the first two months following the death of a loved one.

By doing away with this, critics say that the DSM-5 turned grief into insanity. Defending the decision was Dr David Kupfer, who presided over the DSM-5 taskforce. He says that the previous bereavement exclusion was unhelpful, because it suggested "grief somehow protects a person from major depression", leaving some unable to access help.

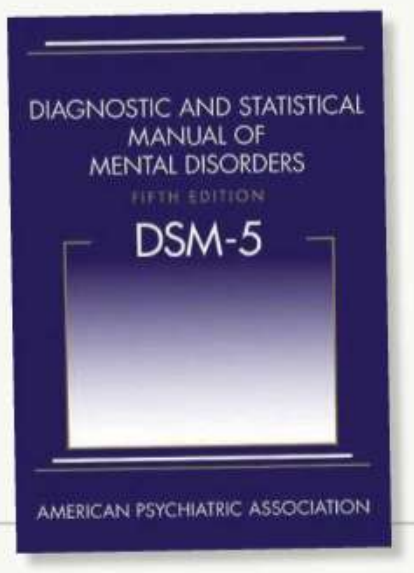
Critics included Dr Allen Frances, a former chair of the DSM taskforce, who believes that the updated manual reduces the ranks of the normal. "Grief becomes 'major depressive disorder', worrying about being sick is 'somatic symptom disorder', temper tantrums are 'disruptive mood dysregulation disorder', gluttony is 'binge eating disorder', and soon almost everyone will have 'attention deficit disorder'," he says.

Frances is not alone in expressing dismay at the DSM's ever-growing reach. "The number of diagnoses has been quietly increasing," notes Prof Simon Wessely of the Institute of Psychiatry, King's College London.

In 1917 the APA recognised just 59 psychiatric disorders. Today, its manual lists nearly 300. The APA itself, however, provides different figures – it says that the DSM-5 officially includes just 157 disorders. But it depends on what you count. Some disorders are excluded as they come under the heading 'for further study', while others are subdivisions of disorders that used to stand alone. Common consensus is that there are 297 disorders in the DSM-5, but what's indisputable is the fact that the DSM has grown fatter. In 1952 it had fewer than 150 pages, while today it's just under 1,000.

ABOVE 'Hoarding disorder' is in the DSM-5, but at what point does a diligently collected trove of treasures become an indication of mental affliction?

BELOW The fifth edition of the DSM lists nearly 300 psychiatric disorders



The DSM has its origins in the military manual *Medical 203*, which was created after WWII to classify the mental health problems of returning soldiers. Previously, there was no 'dictionary' of definitions. What one doctor might call depression, another might label – and treat – differently. The DSM was a way around this. It was intended as a research tool, but what was essentially a detailed textbook soon became a user manual. It really took off in 1980, when the third edition (DSM-III) ushered in a new diagnostic era for psychiatry. It included 80 new disorders and made us familiar with conditions like 'social phobia' and 'major depression'. Critics, though, claim the rise in disorders wasn't based on tangible new evidence – for example, social phobia was simply shyness repackaged. In his book *Cracked: Why Psychiatry Is Doing More Harm Than Good*, psychological therapist Dr James Davies described how the DSM-III's content was determined not by science, but by committee. A group of psychiatrists decided what to include,

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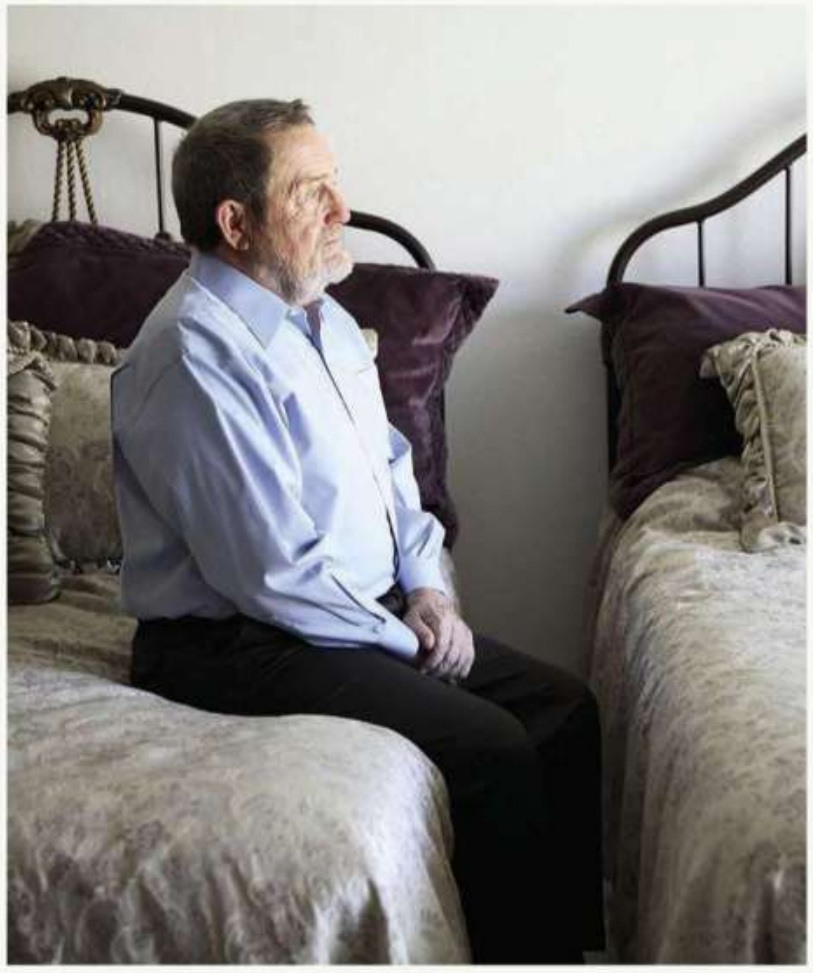
“There are still no lab tests to conclusively diagnose most mental health conditions, including depression”

with the most vociferous getting their way. Davies wrote that a potential symptom was even junked when one of the group pronounced: “We can’t include that... because I do that!”

Higher standards have been applied to later editions. The DSM-5 was compiled by over 160 world-renowned clinicians who evaluated reams of evidence. And yet, there are still no lab tests to conclusively diagnose most mental health conditions, including depression and bipolar disorder. Only a handful of mental disorders, such as Alzheimer’s, have an identifiable pathological basis.



The updated DSM-5 makes people eligible for psychiatric treatment right after they suffer a bereavement, withdrawing a previous two-month buffer following their loss

Opponents say this makes the DSM-5 no more scientifically valid than its predecessors.

"Scientists have failed to find biological markers for nearly all mental disorders, because the disorders for which markers are being sought actually have no sustained reality in anything other than the manuals themselves. This is not to say people don't suffer. It's to say that suffering is less uniform and less easily categorised than these manuals have led us to believe," says Davies.

Prof Nick Craddock, a psychiatrist at Cardiff University, admits the approach is limited. "In psychiatry we rely on the description a person gives and then we have to use that description to arrive at the most appropriate diagnosis. That is the best we can do at the moment."

But while Craddock is critical of the DSM, he supports the need for a system of classification. "People have attacked the DSM's shortcomings as a way of saying the whole notion of psychiatric diagnosis is ridiculous. I'm convinced of the need for a system of diagnosis. It's crucial for helping guide patients towards the best treatments based on knowledge that has been accumulated from research. My own view about the DSM-5 is that it was the wrong time to be trying to develop a new version. It is not better, but it is probably not much worse."

"With brain imaging we can directly observe what's happening in someone with depression"

Wessely goes even further, dubbing the DSM-5 a "public relations disaster" for psychiatry. But chances are that professionals who are critical of the DSM will also be critical of other classification systems, such as the manual produced by the World Health Organization – the *International Classification Of Diseases* (ICD).

"The real pressure is not trying to see more patients and making more diagnoses, it's the opposite," he says. "Most psychiatrists are defending their services to protect their ability to treat those who have very serious recognised disorders, irrespective of the classification system."

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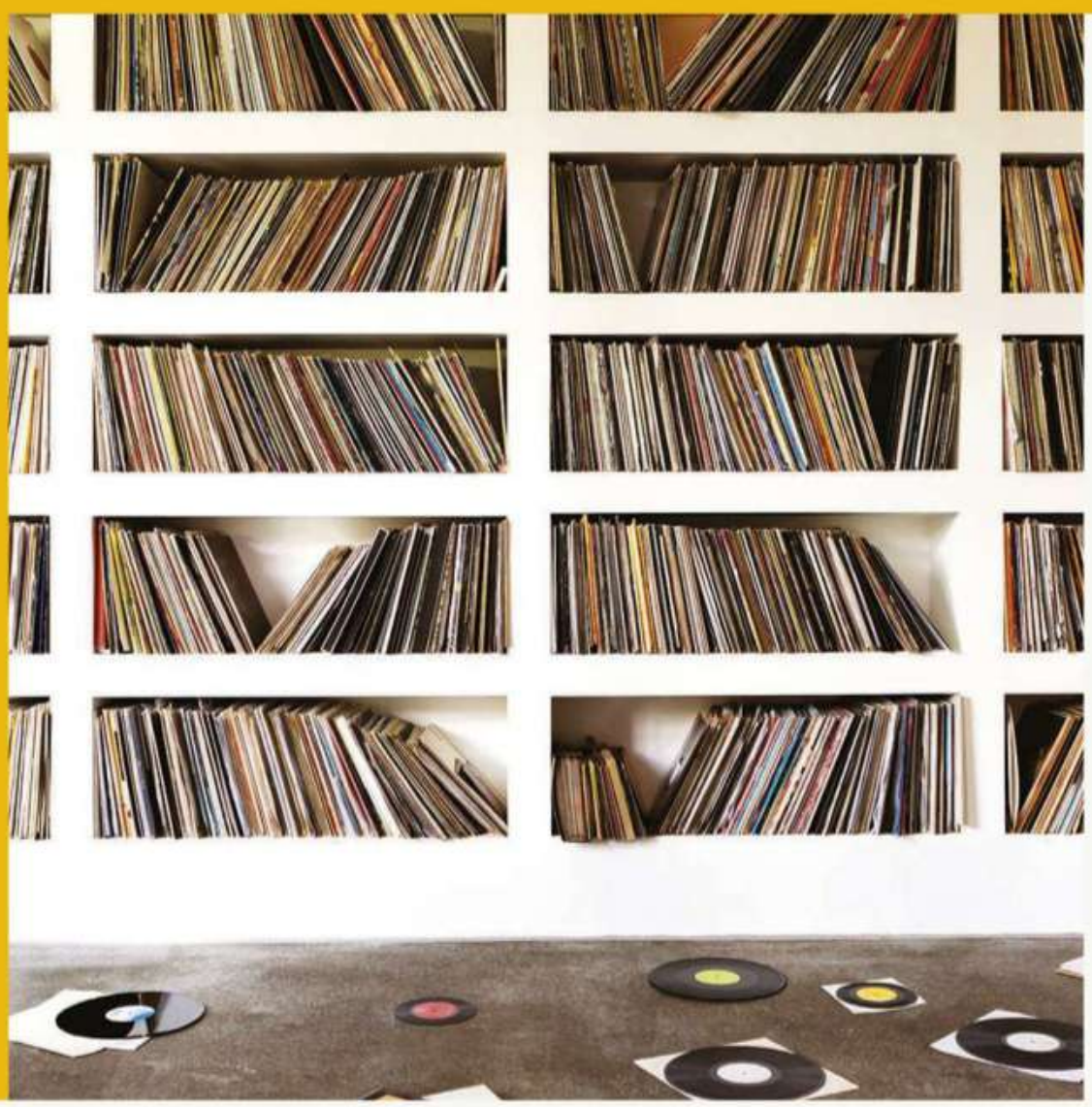


ADDICTION OR HABIT

Is your hobby listed in the DSM-5?

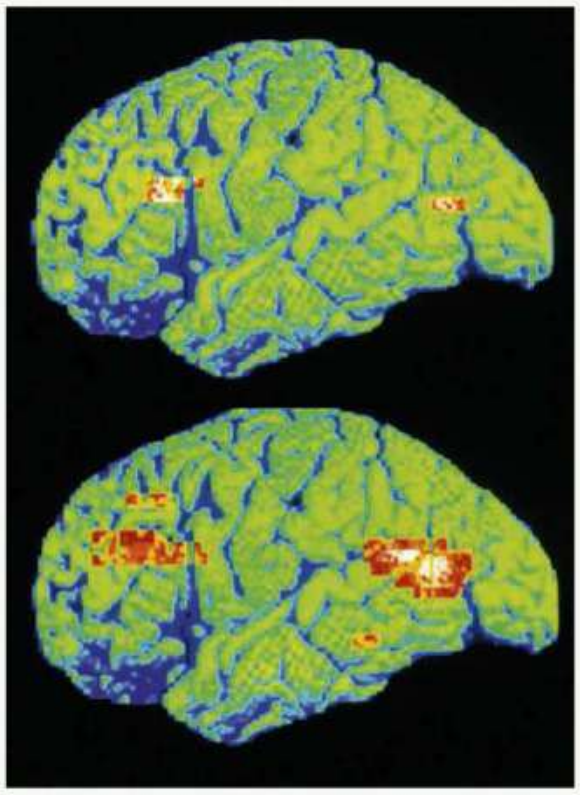
CLUTTER COLLECTORS

Cherishing your record collection may seem harmless but, when taken too far, the DSM-5 views it as insanity. While old editions of the DSM listed hoarding as a symptom of OCD, the DSM-5 gives it a category of its own. The main symptom of 'hoarding disorder' is persistent difficulty parting with items. Up to 5 per cent of people in the UK are afflicted, meaning that an additional three million previously 'normal' people are now classified as insane.

GAMERS

The recurrent use of online multiplayer games, and a preoccupation with them, can result in impairment or distress, according to the DSM-5. Although 'internet gaming disorder' is not included in the manual as a formal disorder, it is mentioned under the heading: 'Conditions for further study'. So, while frequent all-nighters playing *Fortnite* may be okay for now, gamers beware: your days among the ranks of the 'normal' may soon be numbered.

If not the ICD or DSM – what then? Davies hopes that both manuals become obsolete, advocating instead a World Health Organization publication called the *Mental Health Gap Action Plan Intervention Guide*, which includes just 11 categories of disorders. But Kupfer says that the DSM does still have a future. He anticipates "incremental updates" that are responsive to the latest research. The push for new science is backed by the Royal College of Psychiatrists in the UK and the National Institute of Mental Health in the US – both have called for new research directions to improve mental illness diagnosis.



A scan of a healthy brain (top) and a depressed brain (above) show areas of low activity coloured red/ yellow, revealing a marked difference

SEEING THE LIGHT

In many ways, psychiatry remains in the Dark Ages. But advances in neuroscience could put an end to the DSM debate. Craddock likens the situation to cardiology before the invention of the electrocardiogram. "At the moment we are in that '100 years ago phase' in psychiatry, where we are just relying on people's descriptions of how they are feeling as a proxy for what is going on in their brain," he says.

Advances in molecular biology, genetics and brain imaging will change this. "With brain imaging we can observe what is happening in someone when they are struggling to think of something, hearing voices, having a severe depression, or mania," he explains.

Scientists are already using functional magnetic resonance imaging to watch brain activity while people solve problems or view pictures that trigger emotional responses. In the autumn of 2013, imaging by US researchers revealed brain tissue loss in patients with schizophrenia; another study discovered 13 new locations in our genetic code linked to schizophrenia.

Craddock believes that in just 20 years' time, psychiatrists will be able to supplement standard questions about a patient's symptoms and medical history with tests that can objectively diagnose conditions, such as bipolar disorder. "We're about 15 to 20 years away from this. People will look back and think that the particular diagnostic categories in the DSM were all a bit quaint." **SF**

by **JO CARLOWE**
(@jocarlowe)
Jo is a science writer for newspapers such as The Times, The Guardian *and* The Telegraph.

COFFEE DRINKERS

Feeling cranky from a lack of coffee? The DSM-5 considers it to be more than just a caffeine headache. While the previous edition included 'caffeine intoxication' among the more controversial conditions, the newest version has gone a step further, listing 'caffeine withdrawal' under 'caffeine-related disorders'. This is squashed neatly between the sections on alcohol and cannabis.

In order to qualify as 'psychiatrically unwell', your caffeine withdrawal will need to cause meaningful mental anguish or disrupt some key aspect of your everyday life.

ALZHEIMER'S
THE SEARCH FOR A CURE

With one in nine people over the age of 65 suffering from this debilitating disease, the race is on to find a treatment. Could the latest research hold a breakthrough?

by ROBERT MATTHEWS

Todd suddenly lost his way along a familiar path. Like his companion, also in his late 60s, he laughed it off as just a momentary lapse – a 'senior moment'. But it would be their last trek together.

Over the months that followed, Todd became increasingly forgetful and tetchy. Persuaded to see a doctor, he underwent tests and got a diagnosis – he had joined the one in nine Americans over 65 with Alzheimer's disease (AD).

Todd's condition followed the classic trajectory of this most common form of dementia. The regions of his brain involved in short-term memory, planning and thinking were the first to be affected. Then the disease started to spread elsewhere, killing cells in such numbers that his whole brain began to shrink. Personality changes set in, along with problems talking to or even recognising family and friends.

After a few years, Todd became so weak that he became permanently bedridden. Finally, five years after diagnosis, his health suddenly deteriorated and he succumbed to pneumonia – the common fate of most AD patients.

Globally, almost 50 million people are following a similar path as this degenerative brain disease takes hold. And in a cruel twist to the global good news story of increased life expectancy, that figure is set to explode to over 130 million by 2050, as more people survive into old age.

Yet even those grim statistics are eclipsed by the most stark fact about AD. Despite all the breakthrough claims, medical science still has little to offer those diagnosed with this devastating disease. This seems to fly ➤

ALAMY

in the face of the standard story about AD: the cause is known and a cure is within reach.

According to this narrative, AD is the result of a build-up of a sticky protein in the brain. The protein is known as amyloid-beta, and it creates so-called plaques and tangles in brain cells that then malfunction and die. It thus seems clear that in the quest for a cure, the target should be combating amyloid and its effects. For decades that's exactly what researchers and pharmaceutical companies have been doing. But it isn't working.

Veteran AD expert Dr Jack de la Torre of the University of Texas, Austin, puts it bluntly: "The field of Alzheimer's research has reached an impasse after more than 100,000 clinical and scientific papers published in the last 40 years," he says. "There is yet no hope, no effective treatment, and no knowledge of what causes dementia."

BREAKTHROUGH DRUGS

At first, the prospects seemed bright. In 1993, the US Food and Drug Administration (FDA) approved Tacrine, the first drug to be widely marketed for combating the symptoms of AD.

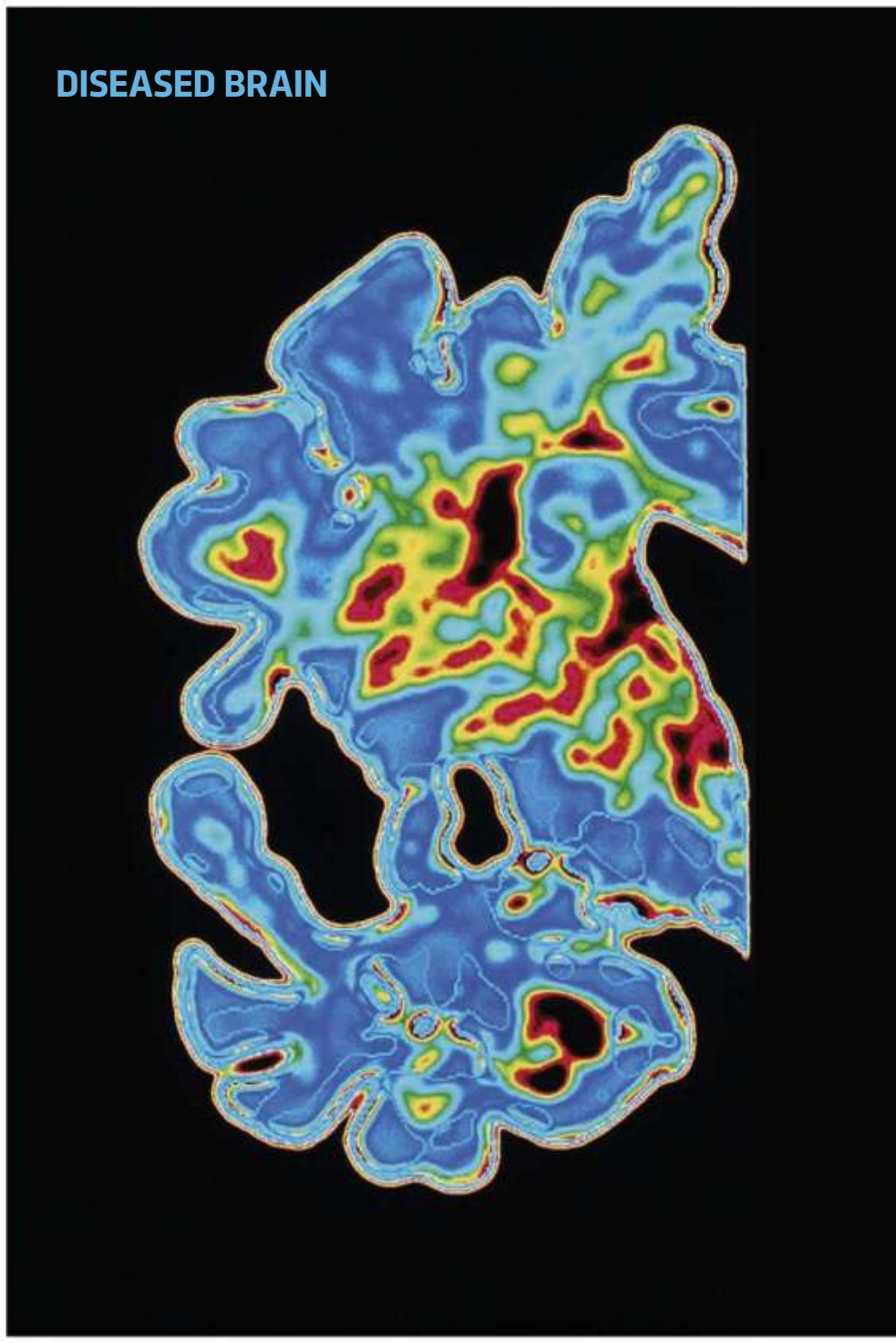
The drug was supposed to compensate for the impact of AD on cognitive ability by boosting levels of a neurotransmitter acetylcholine. But the improvements it produced were modest – and came at the price of serious side-effects. In 2013, these led to Tacrine being withdrawn from the market.

Over the years, around 400 therapies for AD have reached the human trial stage, but almost all of them have failed. Even so-called 'breakthrough' drugs, such as Aricept, have proved only marginally beneficial with most patients.

Hopes that genes would unlock the mystery of AD and lead to a cure have also proved misplaced. During the early 1990s, researchers seemed on the brink of a huge advance with the discovery of a gene that was code-named 'APOE-epsilon4'.

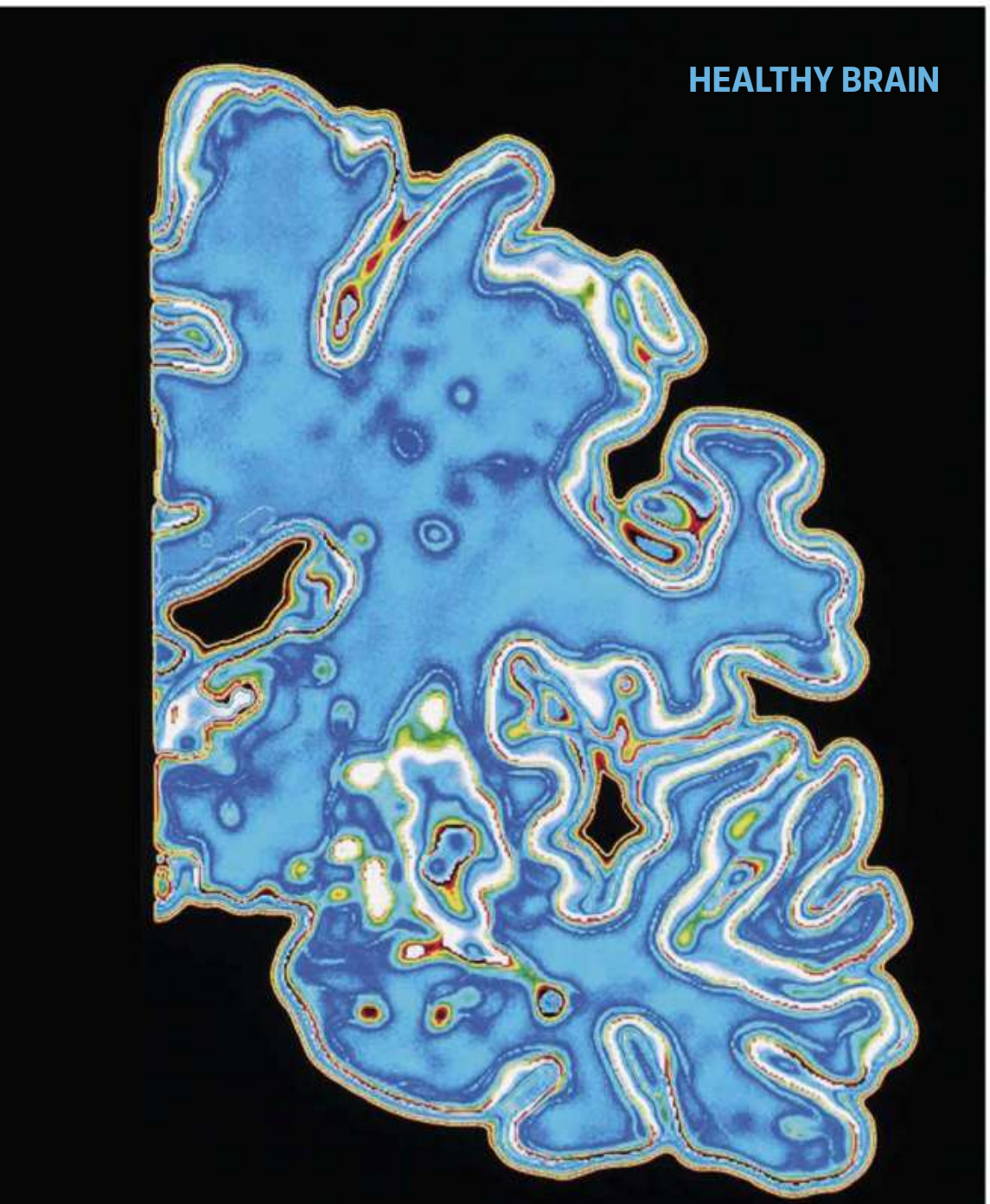
Studies revealed that around one in five people carry a single copy of this gene on their DNA, and as a result face a four-fold higher risk of AD, soaring to 10-fold for the one in 50 carrying two copies. The obvious question was: why?

In 2008, scientists at Case Western Reserve University, Ohio, discovered that the gene seems to affect the ability of brain cells to clear the sticky amyloid protein fragments



RIGHT A computer graphic of a vertical slice through the brain of an Alzheimer's patient (left) compared with a normal healthy brain (right). The brain of the Alzheimer's patient is considerably shrunken, due to the death of neurons

BELOW One in nine Americans over the age of 65 suffer from Alzheimer's disease. Almost 50 million people live with the condition worldwide, and this figure is expected to rise to over 130 million by 2050



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that form plaques. Then, in 2012, the same team made headlines worldwide by showing that an old anti-cancer drug called bexarotene dramatically boosted the cleaning ability of brain cells. In experiments, the drug seemed to clear away plaques, leading to improved brain function. But there was a caveat: those benefiting were mice, not humans.

Using animals as substitutes is problematic with any drug, but has proved especially so with AD – and attempts to confirm the finding failed. Back in 2016 the outcome of the first human study also proved negative.

The story is not quite over yet. Lead investigator Dr Jeff Cummings, of the Lou Ruvo Center for Brain Health in Las Vegas, points out that this was only a small pilot study and that "the observation definitely needs to be replicated and followed up" in a larger trial.

Bexarotene thus joined several other anti-plaque compounds currently in full-scale clinical trials. They include 'monoclonals,' such as solanezumab, designed to seek and destroy amyloid protein like guided missiles. Yet despite being hailed as a massive step forward, even by the UK government, these fell well short of the hype when results of the trials began to emerge.

"In a cruel twist, the number of dementia sufferers is set to explode to over 130 million by 2050, as more people survive into old age"

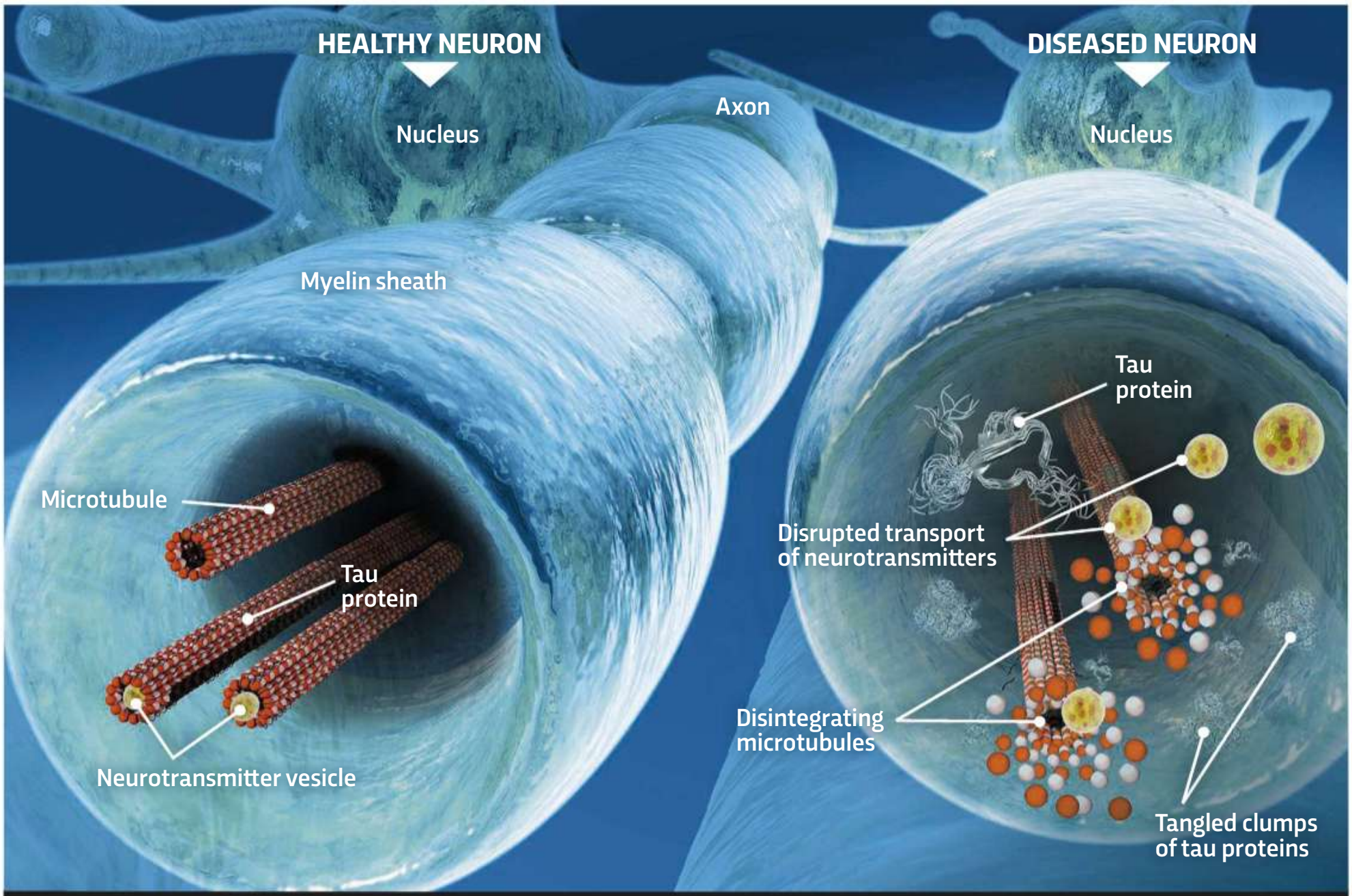
A CHANGE OF DIRECTION

This seemingly endless stream of disappointment has prompted concern that perhaps the decades-long focus on plaques is simply misguided. It's a view backed by an intriguing fact: while most AD patients have high levels of plaque, similarly high levels have also been found in around one-third of people with no sign of dementia at all.

The idea that there's something else involved won a boost in 2016 from new brain-scanning studies by a team from Washington University School of Medicine, St. Louis. These have focused on another brain protein called tau, which plays a role in keeping neurons healthy and tangle-free.

Defects in tau have long been linked with AD, and the team found that levels of this protein may be better predictors of cognitive decline than amyloid protein alone. "What we suspect is that amyloid changes first and then tau," says lead researcher Dr Beau Ances. "It's the combination of both that tips the patient from being asymptomatic to showing mild cognitive impairment."

But some researchers insist the lack of progress in finding a cure demands a more radical rethink. In 2016, the highly respected *Journal Of Alzheimer's Disease* published an editorial with over 30 co-signatories calling for research into the possibility that infections cause AD. The lead author of the article was Dr Ruth Itzhaki of the University of Manchester, who has long suspected that both amyloid and tau protein levels are just symptoms of the true cause of AD. For over 25 years, she and her colleagues have been gathering evidence that agents like the herpes simplex virus lie dormant in the brain for decades, but then burst back into action and attack cells as



In a healthy neuron (left), tau proteins bind microtubules together, ensuring neurotransmitters pass through the vesicle.
In a diseased neuron (right), the tau proteins break down and microtubules disintegrate, disrupting the transport of neurotransmitters

our disease-fighting abilities decline.

If true, this raises the astounding possibility that at least some cases of AD could be treated using standard drugs, such as antivirals.

While many researchers are sceptical of the 'dormant infection' theory, some have given it a cautious welcome. "These observations are interesting and warrant further research," says Dr James Pickett, head of research at the UK Alzheimer's Society. "[But] there is currently insufficient evidence to tell us that microbes are responsible for causing Alzheimer's disease in the vast majority of cases," he adds.

REDUCING THE RISK

While scientists argue the merits of the different theories, evidence is growing that we can all reduce the risk of developing AD. Studies suggest that keeping mentally and physically active in later life, and switching to a 'Mediterranean' diet rich in fruit, vegetables, olive oil and fish can be beneficial. Again, the strength of the evidence has often been hyped, but most of the measures are already known to boost general health and so are worth trying regardless of their impact on AD risk.

"If true, this raises the astounding possibility that at least some cases of AD could be treated using standard drugs like antivirals"

While scientists argue over the direction the quest for a cure should take, everyone agrees about the need to address chronic underfunding of research.

"We have made great strides in treating and preventing many diseases – even major killers such as cancer, heart disease, and HIV/AIDS – when we have made the issue a high priority and the resources available for research," says Dr Maria Carrillo, chief science officer of the US Alzheimer's Association. "Now is the time to do the same for Alzheimer's disease." **SF**

by **DR ROBERT MATTHEWS**
Robert is a visiting professor at Aston University and writes for BBC Science Focus.

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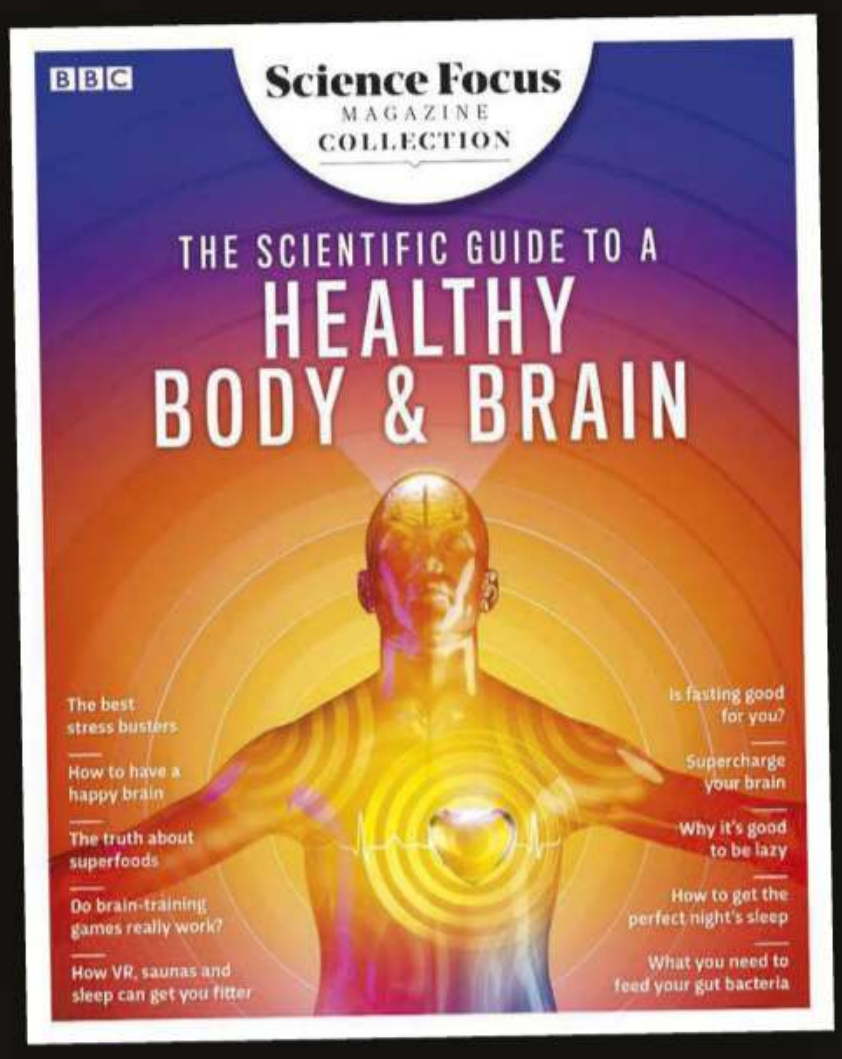
THE SCIENTIFIC GUIDE TO A HEALTHY BODY & BRAIN



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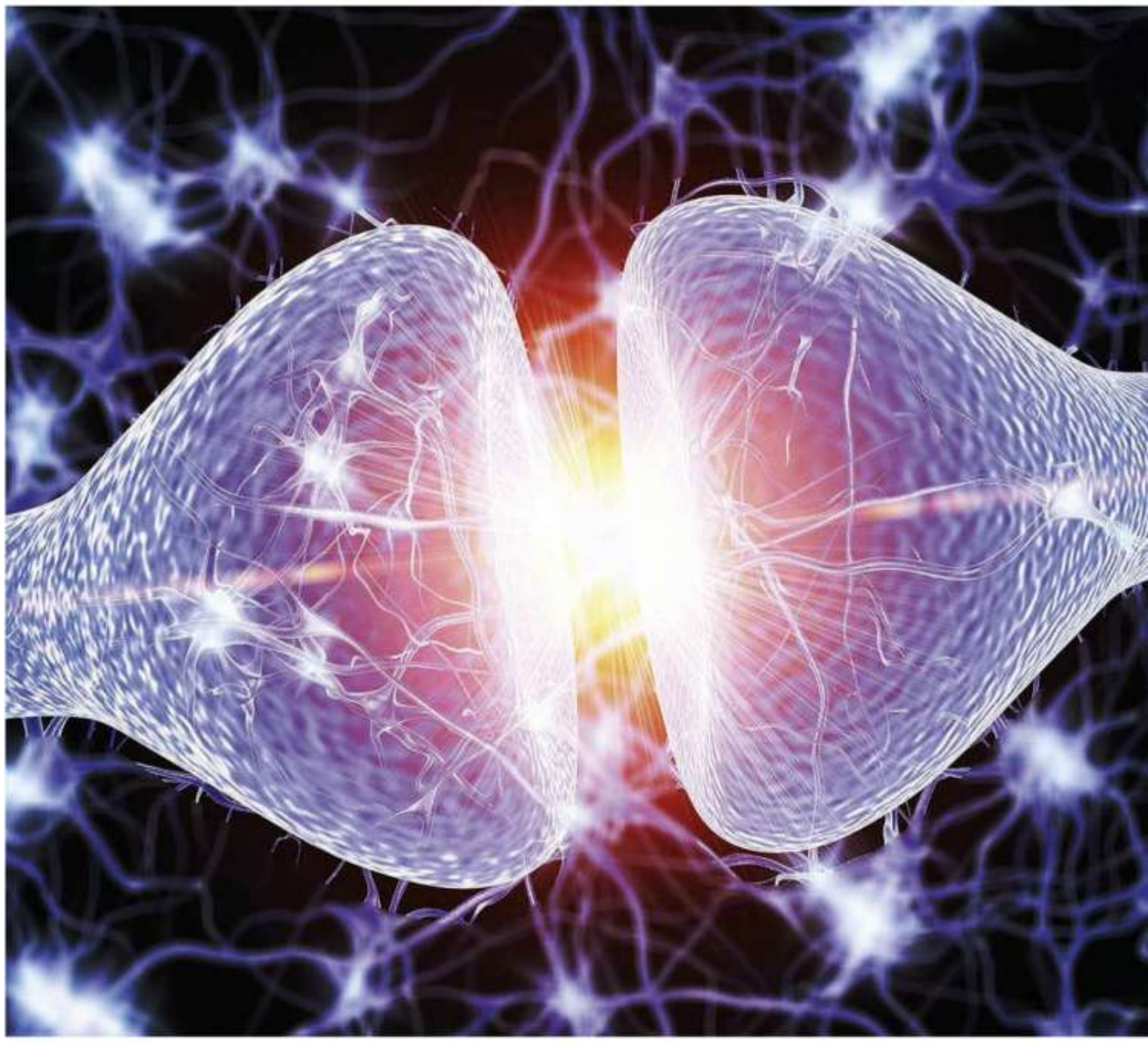
The pursuit of happiness

At any one time, more than 350 million people are living with depression. Now, scientists are trying to flick the neurochemical switch to turn life from a curse into a joy

by ZOE CORMIER



Depression affects an estimated 350 million people around the globe. And this common mental disorder is the leading cause of disability in the developed world, according to the World Health Organization. So what goes on inside our brains to create such malaise?

The idea that depression is linked with an imbalance in the levels of the neurotransmitter serotonin is outdated. Mainstream media has over-simplified how antidepressants work, claiming they simply 'top up' serotonin levels.

While it is true that selective serotonin uptake inhibitor (SSRI) medications, such as fluoxetine, work through the brain's serotonin pathways, this is just part of the story. Conventional antidepressants that act on the serotonin networks are effective for less than half of depressed patients prescribed them.

"Nobody believes in single neurotransmitter hypotheses any more," says Phil Cowen, a psychopharmacology professor at the University of Oxford. "One can't explain depression as one defect in any single neurotransmitter. They may be involved, but they are just part players in a complex system."

Cowen used magnetic resonance spectroscopy to measure levels of GABA, glutamate and glutathione in the brain, in a study published in the journal *Psychopharmacology* in 2015. Although depressed patients had lowered levels of glutathione in the cortex of the brain, this was only one small part of the bigger picture.

ABOVE
Neurotransmitters, such as serotonin, pass across synapses, which are the junctions between two nerve cells (neurons)

BELOW
Antidepressants, such as fluoxetine, are effective for less than half of patients

PEEKING UNDER THE HOOD

The greatest advance in explaining the neurological mechanisms at play in depression is the rise of brain imaging technologies. Analysing changes in blood flow, anatomy, and electrical activity in the brains of depressed individuals has allowed scientists to discover quantifiable differences, such as a reduction in the size of the hippocampus – a region crucial in forming new memories. But even when neuroscientists can find specific 'scar effects' in one part of the brain, this again is just part of the picture: no one brain region is at fault in depression.

"We increasingly see depression as a disturbance of neural circuitry, with the involvement of multiple neurotransmitters, neuromodulators, and anatomical regions," says Cowen.

One popular model is that the limbic system – the so-called 'reptilian' brain, which includes regions such as the amygdala – is overactive, while the prefrontal cortex, which would normally regulate the activity of the limbic system, is underactive.

"The net result of having an overactive amount of fear coming up from the bottom of the brain, and not enough top-down control of it, is that you will look around the world and tend to see nasty things more than other people will," says Cowen.

In other words: depression has a great deal to do with the ways that people perceive disappointments and trauma, and not the nature of the experiences alone. This might sound simple, but take the fact that 65 to 70 per cent of people do not become depressed following a bereavement, a diagnosis of cancer, or another significant form of trauma.

"Many people with depression have what we call a 'negative bias' – they focus on the bad things in life," explains psychologist Prof Catherine Harmer, also of the University of Oxford. This bias means that people in a depressive state are worse at

For those already predisposed to develop depression, feelings of grief can be magnified following traumatic events, such as losing your job

recognising happy facial expressions, slower at categorising and remembering positive self-referential personality words, and worse at remembering positive life events. This creates a cyclical feedback loop that worsens the initial depression.

"Given the same life event or stressor as a non-depressed person, depressed people will take more negative things away from it, which can be a way of just maintaining the symptoms of depression," says Harmer. "Antidepressants break the cycle by helping depressed patients to quickly see things in a more positive light, and over time this leads to a steady improvement."

Evidence of this can be found in Harmer's research, summarised in the journal *Philosophical Transactions B*, which shows that when healthy, non-depressed people are given antidepressants, they are more likely to remember positive information as well. This gives us the biological evidence we need to 'fill the gap' in understanding how treatments for depression actually work.

"With brain imaging technologies, we can now connect the underlying psychological processes that are maintaining somebody's depression with the actual mechanisms in the brain," says Harmer.

"Depression has a great deal to do with the ways that people perceive disappointments, not the nature of the experiences alone"

If the neurological and neurochemical signals of depression might seem dauntingly complex, the root causes are even more so. Depression comes in many different forms, due to a litany of factors. For example, some people may experience happy childhoods, yet be genetically predisposed to develop depression – say, due to a family history of bipolar disorder. At the other end of the spectrum will be individuals without any such biological predisposition, but who suffer terrible trauma and abuse in early life.

"Though these two groups might exhibit similar symptoms, the mechanisms that underlie those symptoms will be different, and require different treatments," says Harmer. "Taking a more nuanced approach will allow us to create more personalised medicines."

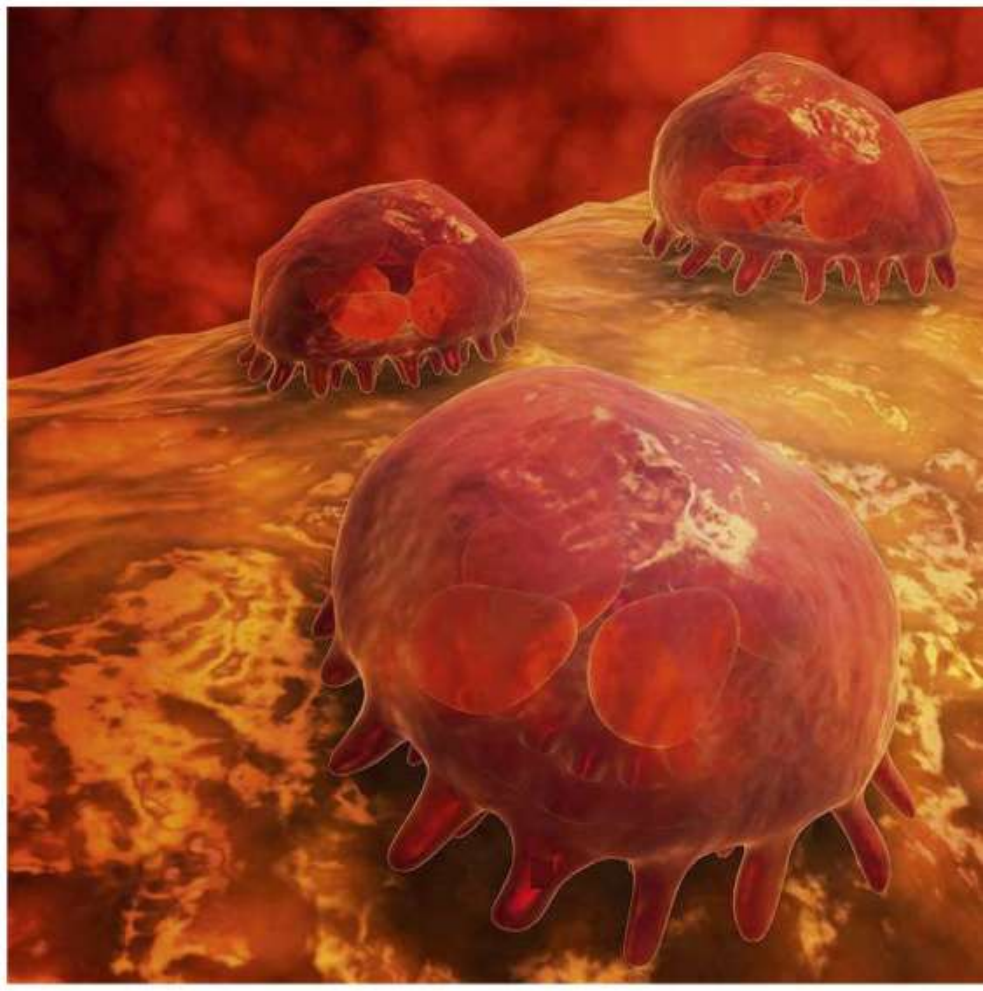
PERSONALISED MEDICINE

You may have heard of this buzz phrase before. One of the hottest ideas in medicine at the moment is the belief that genetic screening will allow physicians to prescribe their patients with drugs that only they will respond to. Less than half of all depressed patients respond to conventional SSRIs on ➔

GETTY IMAGES X2, ALAMY

the first try, and as many as a third do not respond to any drugs on offer today. Not only do we need new drugs we also need ways of knowing if they will work for an individual, lest they waste years taking drugs that do nothing.

In the spring of 2016, the Royal College of Psychiatrists announced that they had formulated a blood test that would identify who would respond to conventional antidepressants based on their blood levels of 'inflammation'. People with heightened inflammation, caused by molecules called cytokines, are less likely to respond to conventional antidepressants, and about a third of people with depression have elevated levels of blood inflammation. This points to one of the most promising new avenues of research: the stress response, which could be a key factor for many forms



RIGHT Microscopic view of macrophages, which are involved in the body's immune response

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LEFT Giving children the best experience possible growing up is one of the most powerful things society can do

of depression. In this new model, the feelings of malaise, low appetite, and fatigue are just the byproducts of a body exhibiting a normal immune system response.

When we are infected or injured, white blood cells called macrophages produce cytokines, which signal to other macrophages to help fight the infection or repair the injury. Cytokines also head to the brain where they trigger 'neuro-inflammation', which brings about 'sickness behaviours', such as fatigue.

This makes sense from an evolutionary point of view because if you are ill it is best to convalesce and not to risk catching new infections. White blood cells will also release cytokines when we are emotionally stressed, leading to the same feelings of fatigue and low mood. In the past, this would be adaptive, but in today's environment, non-lethal threats, such as an empty bank account or an angry boss, can trigger the same response.

In other words, the combination of our ancient biology – primed for fight or flight – with the stresses of modern life has produced an epidemic of malaise. In particular, people who experience abuse and trauma in childhood appear to have elevated baseline levels of inflammation – thus stressful experiences in adulthood tip them over the edge, resulting in depression.

People with high inflammation levels don't tend to respond to antidepressants. But fortunately, there are already drugs on the market that target the inflammatory response for other conditions, such as infliximab, normally used to treat Crohn's disease. Clinical trials with anti-inflammatories are already underway and show promise.

Other new drugs being explored include the psychedelic anaesthetic ketamine, which trials have shown to produce a rapid effect. But the relief from depression is short-lived, so researchers are hoping to identify the underlying neural mechanisms – which involve the NMDA receptors, and not the serotonin networks – to design new drugs that work through the same system. The psychedelic found in magic mushrooms (psilocybin) has also been shown to produce rapid, profound and long-lasting relief from depression.

"But the anti-inflammatory drugs are the most interesting options at the moment," says psychiatrist Prof Glyn Lewis, who is chair in clinical trials and applied epidemiology at University College London.

The power of anti-inflammatories also explains why exercise has been shown to be helpful for people suffering from mild depression. But Lewis's research has also found that people with severe cases of depression are unlikely to benefit from a jog around the park.

"We concluded that advising people with depression to simply take more exercise would not be an effective intervention," he says. Stronger stuff is needed.

Mindfulness is the topic du jour in mental health circles.

"Evidence shows that mindfulness can prevent relapses in people who are well, but were depressed in the past," says Lewis. "But there isn't much evidence it can treat depression on its own."

Ultimately, there is unlikely to be a 'silver bullet' cure for depression – recovery will involve a mix of new drugs combined with a healthier diet and regular exercise, and avoiding stress, alcohol and smoking.

But Cowen says the best thing that society could do, is to try and reduce the overwhelming prevalence of childhood trauma, which is one of the strongest predictors of developing depression in adulthood. "Giving more children the best experience possible growing up is one of the most powerful things we could do."

That, and to erase from mainstream media the idea that antidepressants don't work, lead to suicide, or that drug companies have simply pulled the wool over our eyes with misleading data.

"That is unhelpful for people who are depressed, it makes them feel what they're experiencing isn't serious, isn't real, and that they can be tricked out of it in some way," adds Cowen. "That, frankly, is insulting." **SF**

"Ultimately, there is unlikely to be a 'silver bullet' for depression – recovery will involve a mix of new drugs and lifestyle changes"

by **ZOE CORMIER**
(@zoecormier)
Zoe is a science writer. Her books include Sex, Drugs And Rock 'n' Roll *(£12.99, Profile Books Ltd).*

GET SMART

HOW TO IMPROVE YOUR MIND

Is your brain feeling the strain? Can you boost your mental performance? Here are some of the gadgets and techniques that claim to do just that…

by CHRISTIAN JARRETT

NEUROSKY / GETTY IMAGES

Could brain stimulation devices help you unlock more of your mind's potential?

You're shopping on the main street. After passing the optician and the pharmacy, you reach the brain stimulation store with its shelves and racks filled with headbands and skullcaps. The items sold here are designed to boost your mental performance or alter your mood by manipulating the activity of your brain.

Sounds far-fetched, doesn't it? In fact, the technology is already here and on sale in a variety of forms – but does it really work and is it safe?

One online company called foc.us is selling a brain stimulation device that it claims can help you play video games better and clock up high scores. Meanwhile, towards the more physical end of the spectrum, there is the Halo Sport 2 headband, which is said to improve your ability to learn the movements necessary to play sports or musical instruments. The San Francisco start-up company behind the Halo Sport 2 claims it will elevate your cognitive performance via so-called 'neuropriming.'

Another company, called NeuroSky, offers the MindWave Mobile 2 headset and associated apps, some of which it claims "may help users improve control of attention and relaxation skills in everyday life."

HOW DO THEY WORK?

The foc.us and Halo devices use weak electrical stimulation to either increase or decrease neuronal activity in the brain near where electrodes are placed on the head. This is known as transcranial direct current stimulation (tDCS).

Electrical currents are delivered through the scalp and into the brain via electrodes – an anode and cathode. Applying current through the anode is thought to increase the excitability of neurons, while cathodal stimulation has the opposite effect. It is believed that tDCS alters the level of neuron activity so that they are more or less likely to fire. It's also thought to change how neurons behave at synapses – the gaps over which neurons communicate with each other.

The claims made by the various companies touting these devices are rather vague. They refer to increasing your brain's plasticity and

ABOVE LEFT A father and daughter make-believe at receiving communications via their homemade helmets

ABOVE The Halo Sport 2 headset (top) is said to improve your muscle memory, while NeuroSky's MindWave Mobile 2 headset (bottom) may help you develop your concentration skills

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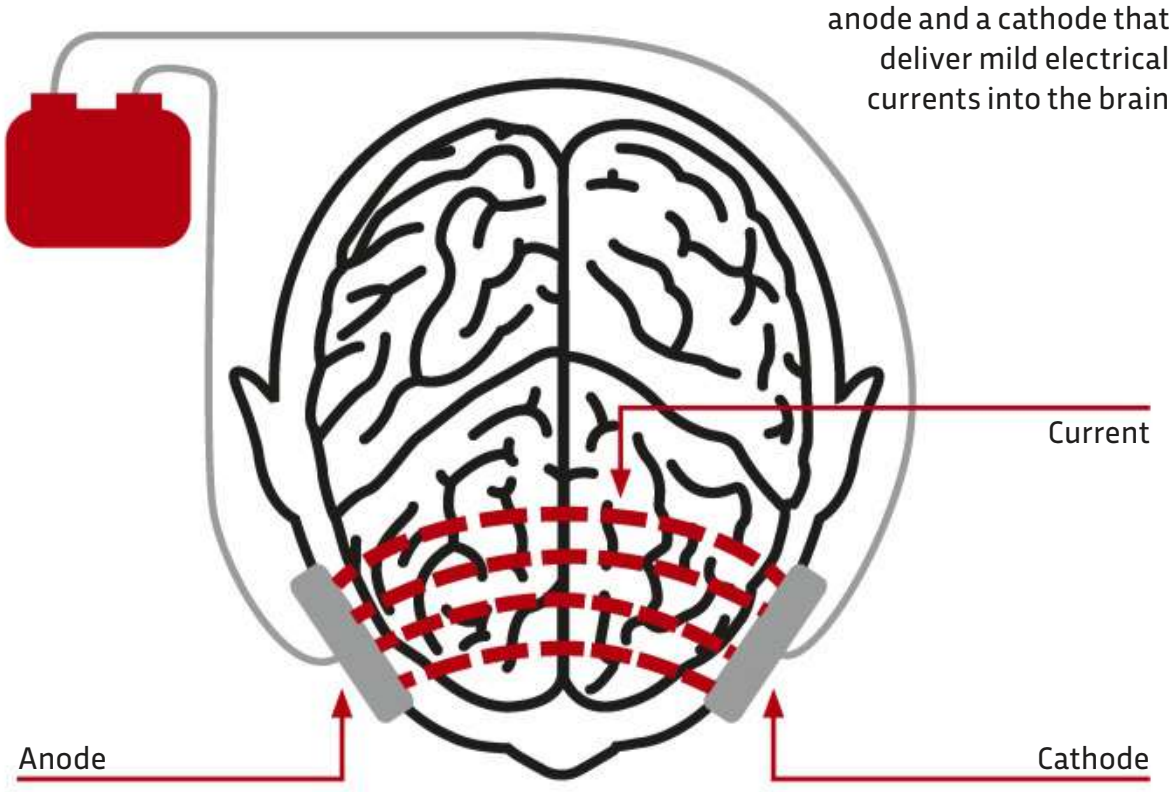


"Zapping your brain with tDCS can improve memory, problem-solving, language and even social skills"

enhancing your mental performance. This may sound like nonsense, but there is peer-reviewed evidence suggesting that tDCS is associated with mental enhancements in healthy participants, the precise nature of which varies according to the site of stimulation.

Researchers have shown that zapping the brain with tDCS can improve memory, language learning, problem-solving, visuospatial processing (such as the ability to detect targets on a screen), and even some social skills. But activities you do after brain stimulation – even going for a walk – can potentially reduce or reverse the effects. And, sceptics argue that few of these studies have controlled sufficiently for placebo effects.

The NeuroSky headset and apps are based on different technology. Devices like these record your brain's electrical activity (the brainwaves) then feed this information back to you together with certain sounds and visuals. The idea is that you can learn to control the frequency of your brainwaves and increase the amount that you generate in the alpha range (8Hz to 12Hz).

NeuroSky claims that increasing your alpha brainwaves is associated with a range of cognitive benefits, especially enhanced short-term memory. But the evidence here is contentious. Many studies that are fully randomised and placebo-controlled have failed to observe any benefits from alpha training. Sceptics say using devices like these amounts to little more than a form of tech-assisted relaxation.

The only things at risk from the NeuroSky feedback device are likely to be your wallet and your schedule. Interestingly, the simple act of closing your eyes is known to increase brainwaves in the alpha range, so this is not a dangerous effect.

The situation with tDCS, and devices that rely on it, is more complicated. While there have been no documented cases of serious adverse effects in over 100 studies, experts have issued several warnings about the possible risks of the technology. This includes the fact that the optimal dose of electricity is different from person to person. When using a device at home, there's no way for you to know how much power you'll need.

Another factor is that the long-term effects are unknown. Besides the risk of headaches or scalp burns, at least two studies have shown that by enhancing mental agility in one domain, ➲

DIY BRAIN STIMULATION

Some brain enthusiasts are taking matters into their own hands by making their own stimulation devices. But are they safe?

It's not that complicated to create your own tDCS device, and there are plenty of videos online to show you how it's done. Perhaps it's little wonder that a community of do-it-yourself brain-zapping enthusiasts has developed.

For example, there's an online subreddit of over 8,400 members who share tips and articles about the technology. One article worries about foc.us, noting they've had stock issues with some older models of one of their headsets.

Part of the reason there is so much enthusiasm is that media reports are biased. After analysing press coverage of tDCS since 2006, a group of Canadian neuroscientists found that most reports focused on the benefits of brain stimulation without noting the potential drawbacks. The team called for more balanced reporting on brain stimulation. Indeed, experts warn that the science behind brain stimulation is still immature, and the long-term effects of its use are still unknown.

TRAIN YOUR BRAIN

Forget brain-training games and apps, cognitive psychologists and neuroscientists have other ideas for how to increase your IQ

It's well known that exercise can help you stay in shape, lose weight, and tone up. But it's also been shown to protect us from forgetfulness, and improve thought processes and problem-solving.

Just like your body requires a good workout, as you get older your brain needs help staying active. Regularly exercising your brain cells is key to keeping sharp. After all, neurons can live for over 100 years and they need to be nurtured.

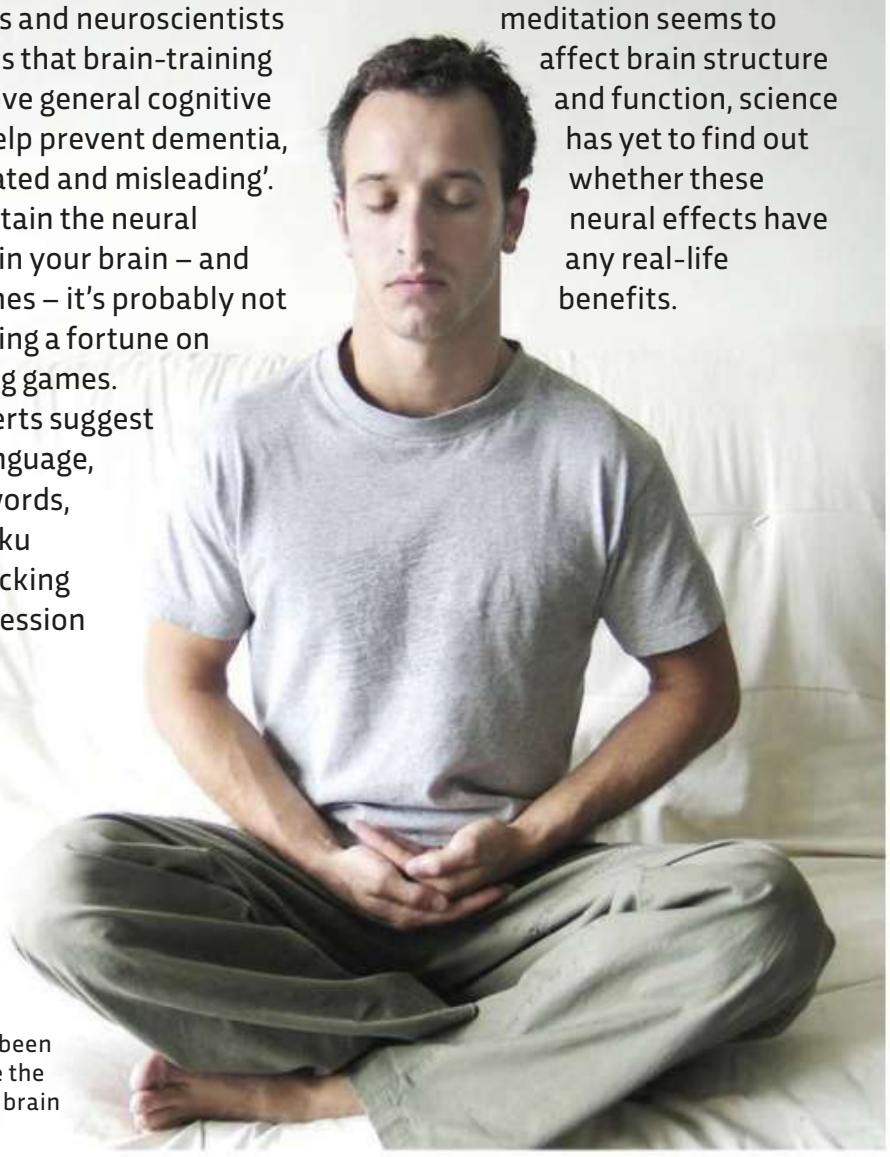
But, recently, we've been inundated with adverts for brain-training games claiming to keep our little grey cells in prime condition. The big question is: do they work?

The verdict is still out. Most evidence suggests that you only improve on the specific tasks in the games, rather than being beneficial to your all-round IQ. Because of this, a group of leading cognitive psychologists and neuroscientists say the claims that brain-training games improve general cognitive abilities or help prevent dementia, are 'exaggerated and misleading'.

So to maintain the neural connections in your brain – and make new ones – it's probably not worth spending a fortune on brain-training games. Instead, experts suggest learning a language, doing crosswords, solving Sudoku puzzles, or kicking back with a session of *World Of Warcraft*. That's right, next time you get scolded for always playing video games, your comeback is that they have been shown to improve problem-solving.

Research also shows intriguing evidence that mindfulness meditation can change the physical structure of the brain, more than regular activities, specifically the rostrolateral prefrontal cortex and dorsal anterior cingulate cortex; areas that are involved in thinking about ourselves and monitoring our own behaviour.

Around a decade ago, neuroscientist Richard Davidson at the University of Wisconsin scanned the brains of Buddhist monks who practise mindfulness and found their brain activity patterns were significantly different from those of untrained students used as 'controls'. However, while meditation seems to affect brain structure and function, science has yet to find out whether these neural effects have any real-life benefits.



Mindfulness meditation has been found to change the structure of the brain

you also impair performance in another.

Based on these uncertainties, experts have begun to ramp up their cautionary rhetoric. Dr Nick Davis, a neuroscientist at Manchester Metropolitan University, published a paper arguing that tDCS shouldn't be referred to as a non-invasive technology. "Any technique that directly affects brain tissue to generate such powerful, acute, and long-lasting effects should be treated with the same respect as any surgical technique."

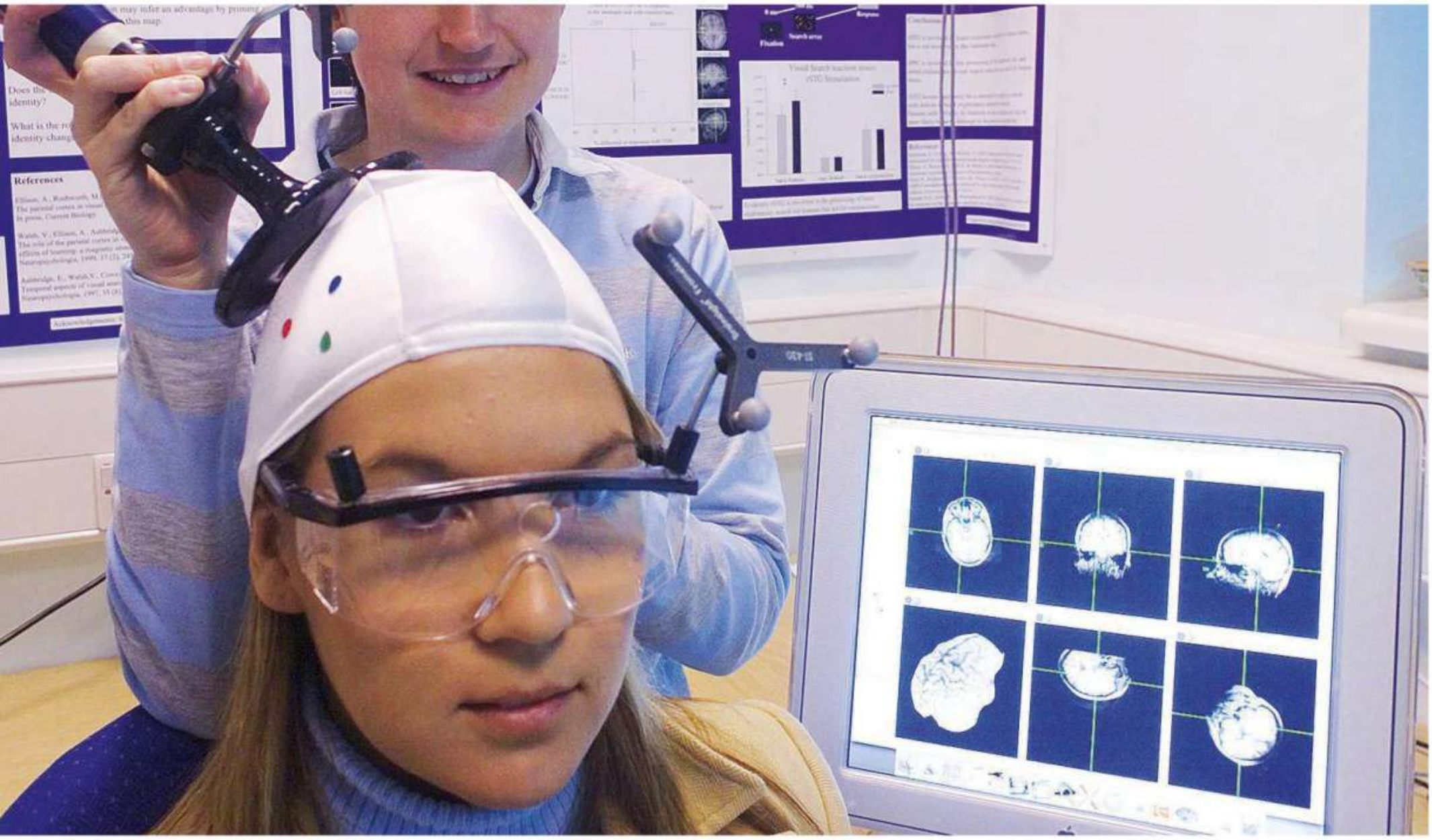
Others have likened the risks of tDCS to those associated with pharmaceutical drugs. "Meddling with the tDCS dose is potentially as dangerous as tampering with a drug's chemical composition," wrote Prof Marom Bikson at the City University of New York. Other concerns are more ethical and philosophical. By using a brain stimulation device to alter your social skills, are you changing your identity? If we can use these gadgets to boost our mood at will, might we lose our drive to fight injustice? Could we become addicted? Some have also raised the spectre of unwanted brain stimulation. Choosing to enhance our brains with a headset is one thing, but what if such interventions were imposed on criminals to correct their immorality, or made compulsory for pupils struggling at school?

OTHER TECHNOLOGIES

Alpha-based neurofeedback and tDCS are not the only tricks in town when it comes to real-life thinking caps. Another technology that shows promise is known as transcranial magnetic stimulation (TMS), in which a magnetic field is used to alter neuronal function.

Although it's more expensive and less portable, TMS – like tDCS – has been reported to have a number of positive effects, especially as a potential treatment for depression and chronic pain. One study even claimed that TMS can

"Any technique that directly affects brain tissue should be treated with the same respect as any surgical technique"



A patient undergoes TMS brain mapping in which a magnetic field is used to alter neuronal function

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unlock hidden savant-like skills in all of us, such as the ability to count a large number of objects in an instant.

But the evidence base is preliminary. UK health advisory body NICE says TMS may be used with normal arrangements for clinical governance and audit. In relation to pain management, it has approved TMS as a treatment for migraines but recommends it is only provided by headache specialists. This has not stopped commercial handheld devices appearing on the market.

The sTMS mini system is made by Californian company eNeura, and is touted as "a clinically proven, non-drug option for the treatment and prevention of migraine for adolescents and adults". It is revealing to note that the evidence for its effectiveness comes from only one small manufacturer-sponsored study and post-marketing surveys.

Finally, there is one other real-life thinking cap that deserves a mention. Before his death in 2018, neuroscientist Michael Persinger claimed his God Helmet could help wearers achieve union with the Almighty. Like TMS, it delivers magnetic fields to the brain, but they are far weaker and of a different kind. In fact, psychologist Craig Aaen-Stockdale has pointed out that the magnet on your fridge is 5,000 times stronger than the God Helmet. Perhaps it's no surprise that a study by Swedish researchers found no evidence that a device similar to Persinger's was able to help wearers have any kind of enhanced religious experience. Persinger said the Swedish device wasn't working properly.

PROCEED WITH CAUTION

Although the commercial release of brain stimulation devices is arguably a little premature, it's almost inevitable that their use is going to become more widespread. Looking ahead, there are likely to be both clinical applications of these devices and lifestyle, or performance-enhancing products.

In a clinical context, researchers are busy conducting more robust, controlled trials to establish what kind of applications are effective, and how best to apply the technology safely. But, when it comes to brain stimulation in our daily lives, the outlook is more unpredictable. There will undoubtedly be a lot more commercial hype about the benefits of technology, and it will be difficult to control how people use it.

Whether used as a clinical tool or to boost performance, it's worth remembering that the brain stimulation devices of today or tomorrow are unlikely to offer a quick fix. It's better to see these devices as offering a technological tailwind, giving a boost to our hard work, whether that be in the context of studying, sports practice, or rehabilitation from illness. **SF**

by **DR CHRISTIAN JARRETT**
(@Psych_Writer)
Christian is a neuroscientist and author of Great Myths Of The Brain *(£15.99, Wiley-Blackwell).*

How to build a BRAIN

It's the question on everyone's lips – when will machines learn to think for themselves? We get the low-down on the projects trying to create brains that run on artificial intelligence

by PETER BENTLEY

Renowned code-breaker and mathematician Alan Turing famously said in 1950: "I believe that at the end of the century the use of words and general educated opinion will have altered so much that one will be able to speak of machines thinking without expecting to be contradicted."

Turing was ahead of his time. But perhaps he was only a few decades out. Today, research groups and tech companies are actively pursuing the dream of making a brain inside a computer. Some try to understand how brains work and produce software components that might duplicate different brain functions – a module to understand text, another for planning, another for short-term memory. Some try to exploit the vast data available and use statistics and powerful computers to infer knowledge. Some try to create detailed software models of millions of neurons and virtually connect them in the same way that our own brains are comprised from billions of neurons. Are these machines thinking? It would have been fascinating to ask Turing and see what he thought.

BIRTH OF THE ARTIFICIAL BRAIN

The pursuit of artificial intelligence (AI) is not new. Even before we created the first programmable computers, we were imagining that one day we might build an artificial mind. Neurophysiologist William Grey Walter was one of ➔

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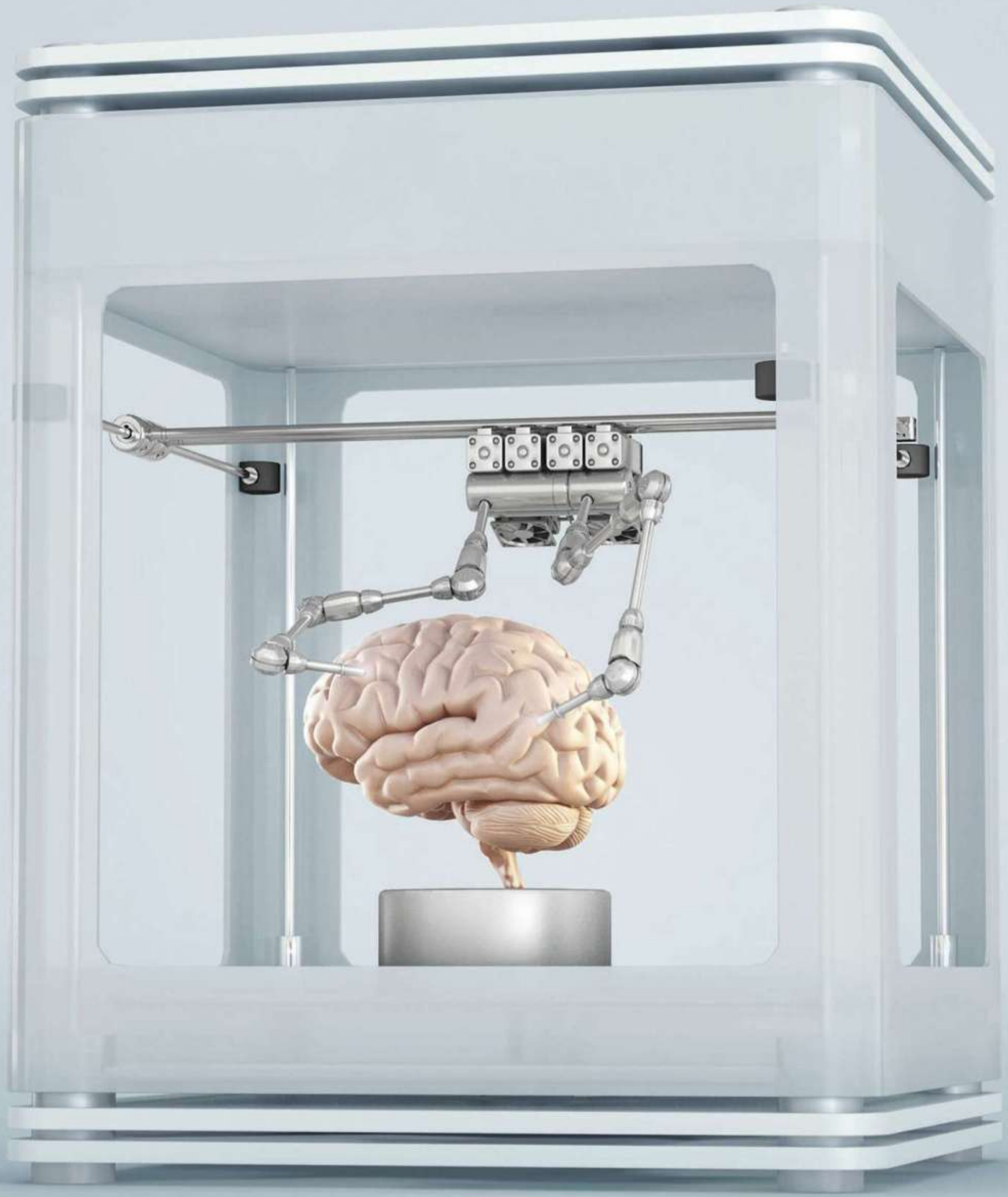
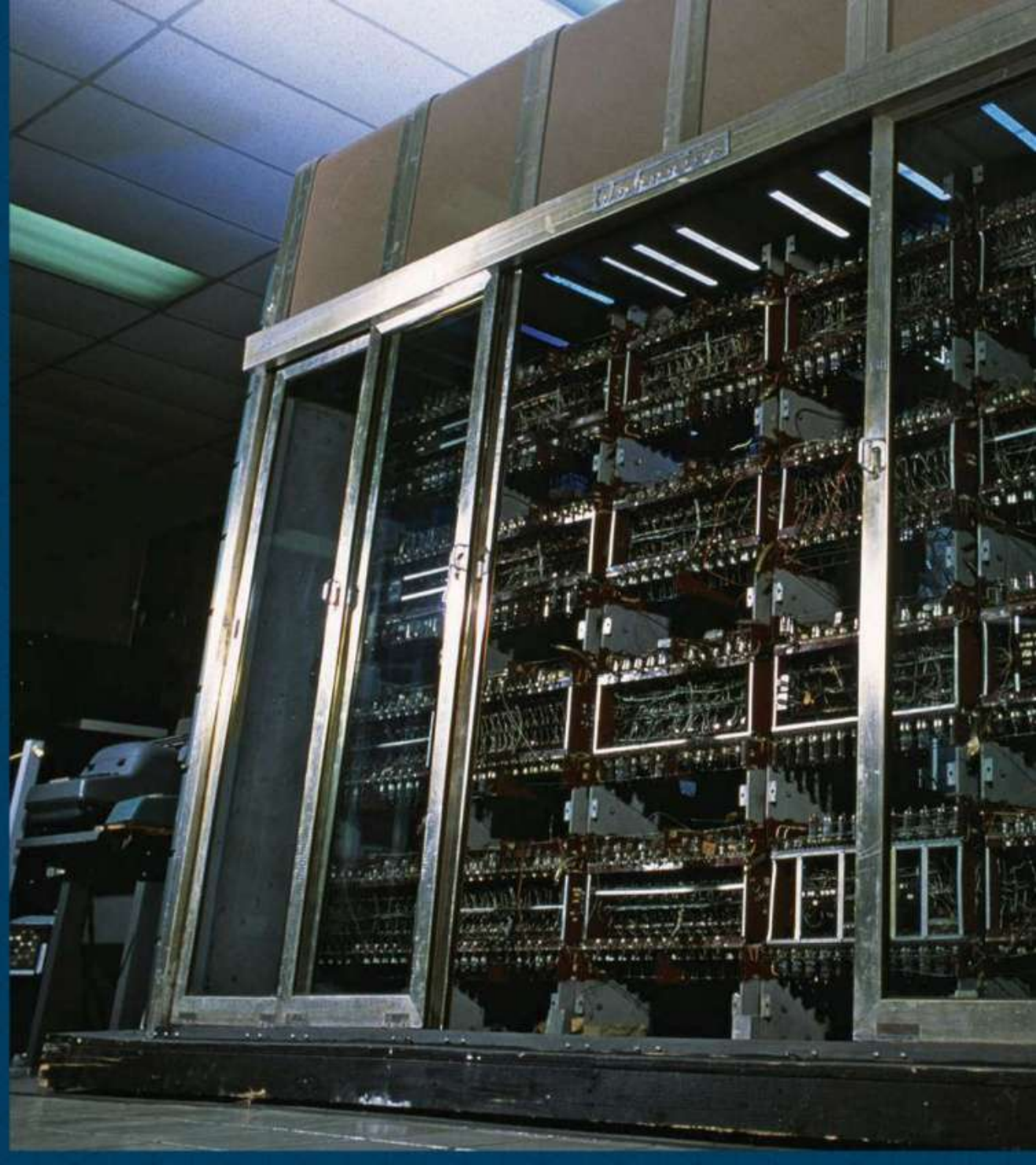
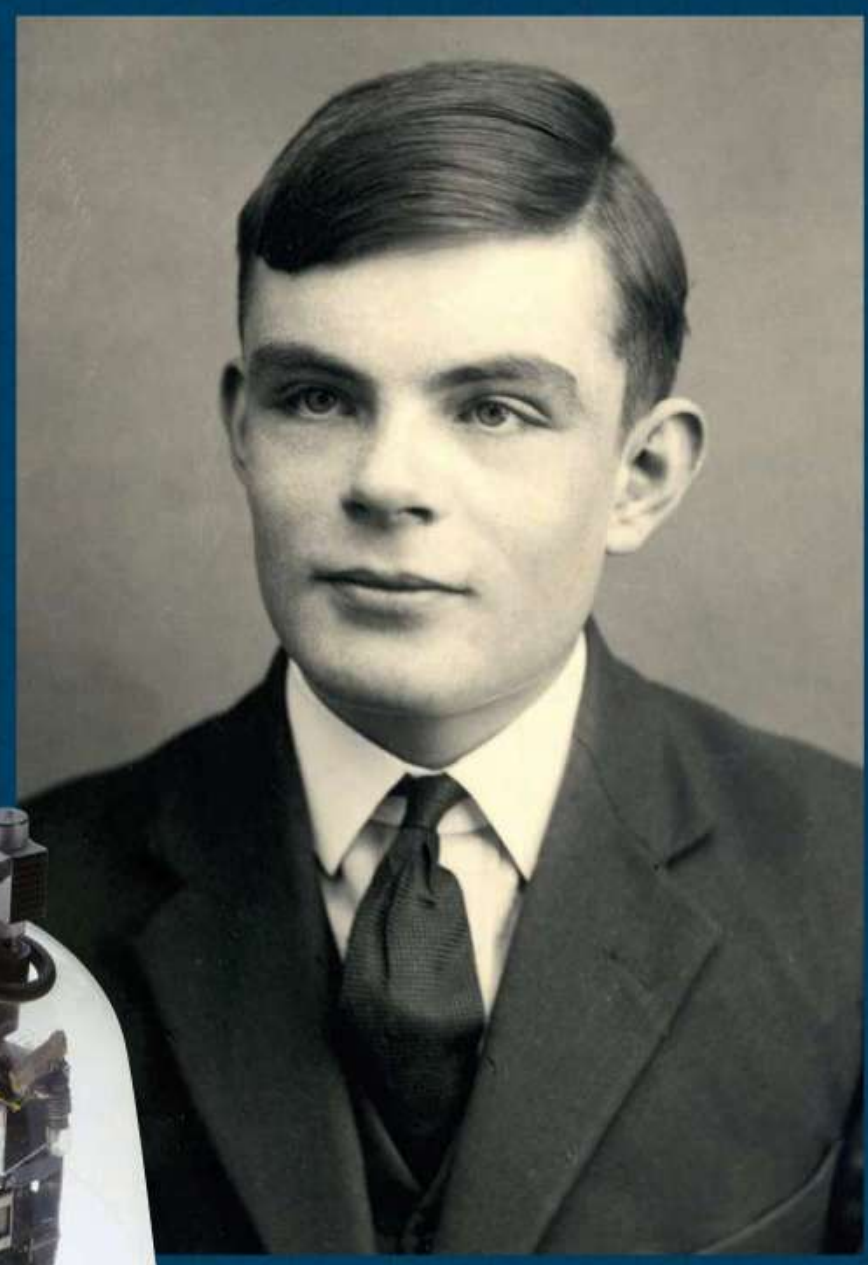


the earliest to have this idea. In the 1940s, he pioneered brain-scanning technologies for medical use, and also built several robot tortoises that could follow a light and back away from obstacles. Just like biologists study animals to show that even a small number of electronic brain cells could exhibit complex behaviours, Walters studied these robot creatures.

As the first programmable computers were being designed in the late 1940s, engineers naturally compared their digital devices to brains. The first easy-to-read description of how to build a programmable computer was written by a mathematician called John von Neumann. Amazingly, he frequently refers to the human brain in his report. He talks about 'organs' in the computer, and how they would perform functions similar to "neurons in the human nervous system". He even tries to explain each major part of the computer in terms of the different kinds of neurons that had been discovered at the time. The von Neumann architecture became the blueprint for almost every computer built since then.

As the years progressed and we tried to write software that made our computers behave in more brain-like ways, we soon realised that biological brains are incredibly intricate. Our computers were built as automatic calculating machines, and because of this they can solve maths problems extremely quickly – much faster than us. But our brains are parallel 'understanding machines' that make sense of vast amounts of dubious information at the same time in order to discover useful new information and relationships about the things around us. Conventional computers are extremely bad at that kind of thing – when the numbers are a little bit wrong or incomplete, their answers are very wrong. We are quite capable of holding a conversation with someone in a crowded room and picking out their replies among a hundred other voices nearby. All a computer hears is noise. Our brains can happily enable us to control thousands of muscles as we run across rough ground, hum a tune, and think about a difficult problem at the same time. Our computers struggle to do any one of these competently. Despite the amazing things we see in science-fiction movies and the predictions we hear about, we still cannot make clever artificial brains.

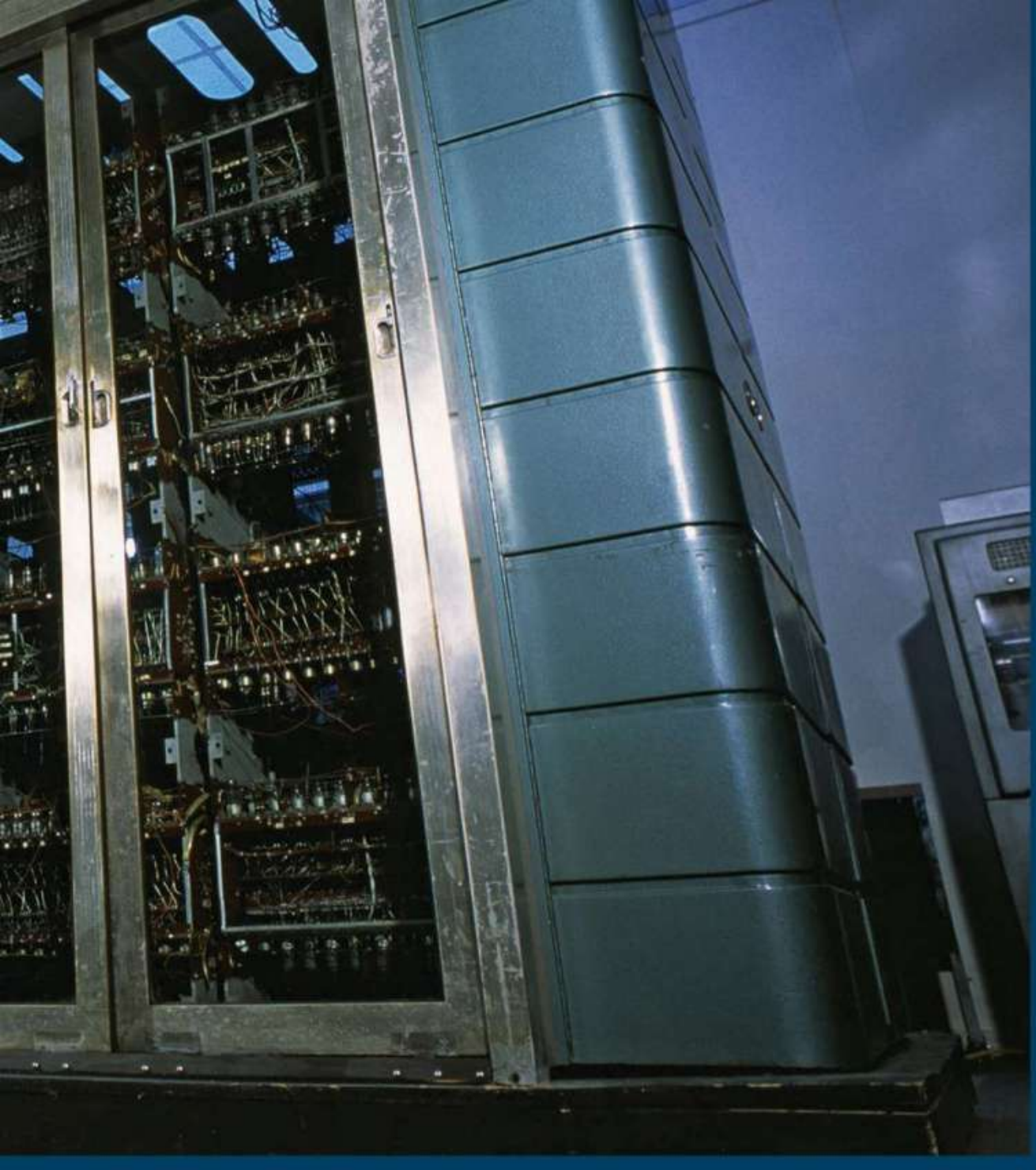




ABOVE The JOHNNIAC was an early computer based on a concept developed by mathematician John von Neumann

RIGHT Alan Turing is credited with conceiving modern computing and cracking the Enigma code

BELOW A robot tortoise designed by neurophysiologist William Grey Walter in the 1940s



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“Despite the things we see in science-fiction movies and the predictions we hear about, we still cannot make clever artificial brains”

THE CHALLENGES

Today, we are able to make robot dogs that run, robot birds that fly and even robot people (that look a little creepy). But they are all stupid. None have much more intelligence than a fruit fly – and most have considerably less.

This is why we still do not have reliable robot assistants that wash our windows or fight fires. The real world is a complicated place. Even the technological marvel of the last 10 years, the self-driving car, is not truly intelligent. It combines radar sensing of its vicinity with detailed maps and GPS to figure out where it is and what to avoid. If the map is wrong or the radar sensor is disrupted by bad weather, the only thing the car knows to do is stop. Even a bee with its microscopic brain can navigate around its world better than our self-driving vehicles, and the bee has no roads to follow, and no maps to check its position.

Making a computer brain has turned out to be a tremendous challenge. The problem is that there are so many unknowns. “Think of something like a novel or a movie,” says Prof Peter Dayan, of the Max Planck Institute for Biological Cybernetics. “We do not know how structured information about complex entities like these are represented in the activity of neurons. On a completely different scale, we also do not know the nature of bottom-up and top-down interactions in the cortex. But every scale has its own fascinating unsolved problems!”

CLEVER HARDWARE

The state of the art in artificial brains uses very complicated software and specialised custom-designed computers to try and duplicate the workings of biological neurons. One pioneer in this area is Prof Steve Furber, from the University of Manchester, and originally the principal designer of both the BBC Micro computer and the ARM microprocessor (the chip at the heart of millions of mobile phones around the world).

For more than a decade, Furber has devoted his considerable energies to the creation of SpiNNaker – a special computer made up of a million processors, all working together to simulate a billion neurons – that’s 1 per cent of the neurons in the human brain. In the last few years, the SpinNNaker project has joined forces with the EU Flagship project known as the Human Brain Project. Progress has gone well, according to Furber. “As of 1 April 2016, we had an operational machine with 500,000 ARM cores,” he says. “By the end of 2016 we had around 800,000 cores. We continued to expand this and by the end of 2018 hit the ultimate goal of a million cores. With 500,000 cores we can model up to 125 million neurons; with 800,000 cores 200 million neurons.” With a few software upgrades, those numbers should creep ever closer towards the one billion neuron target.

SpiNNaker, and other computer architectures similar to it, are being developed as research platforms, to enable computer engineers and neuroscientists to gain deeper insights into how our brains work. In the same way that aircraft engineers test models of aeroplanes in a wind tunnel, these scientists develop ➲

scaled-down and simplified models of brains inside these computers in order to get a better understanding of how the human brain functions.

"The main advantage of [SpiNNaker computing] is the ability to explore the behaviour of neural networks without running into computational constraints or very long run-times," says Furber. "I see the platform being used for a range of purposes, for example, biologically informed models, such as whole mouse-brain models, cortical surface models and spiking Deep Networks for energy-efficient machine learning applications."

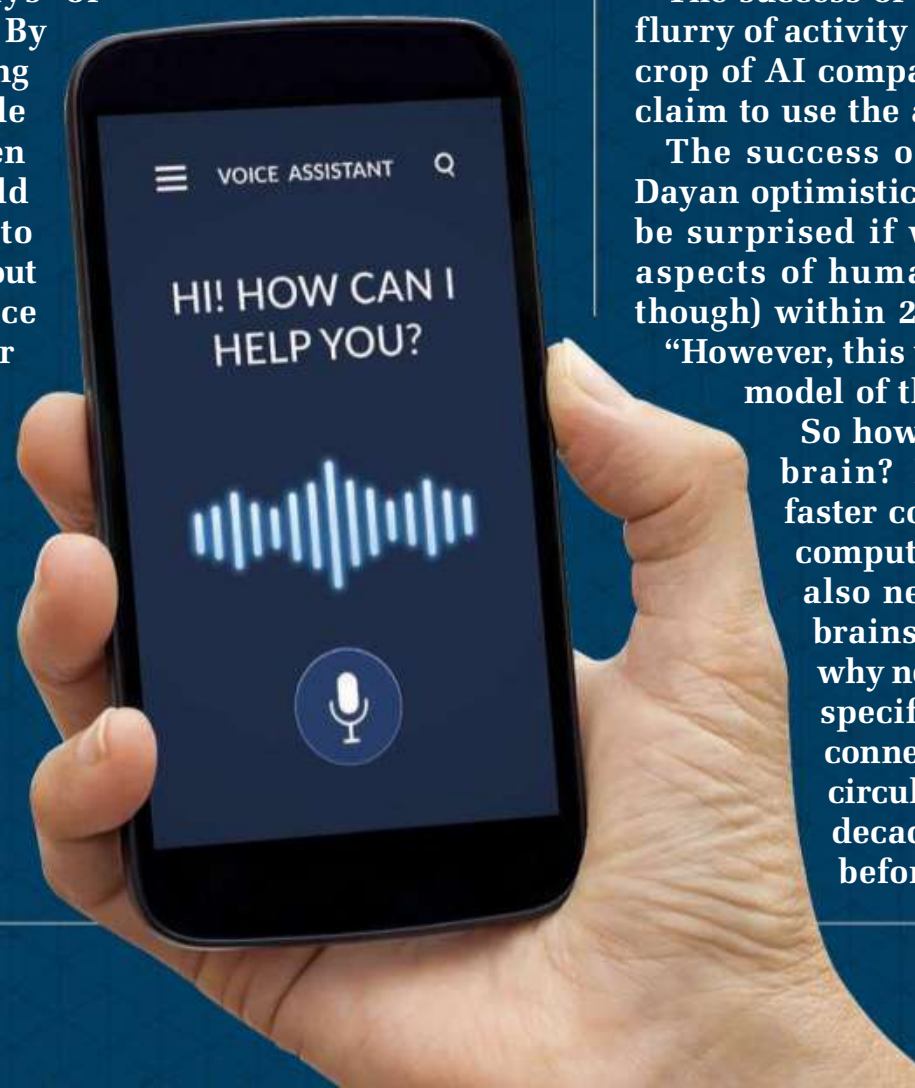
ARTIFICIAL NEURAL NETWORKS

While we may struggle to understand how brains work, a lot of progress has been made in the use of simpler models of the brain. Artificial neural networks, and their fashionable variety known as deep learning networks, are the latest things in AI.

The first models of neural networks were created by AI pioneers in the 1940s, using electronic circuits. Soon the first programs were created to demonstrate that when two neurons fire together, the connection between them is enhanced. The artificial neural network fell out of fashion for some years until new kinds of networks were invented in the 1980s.

Suddenly there were new ways of connecting these artificial neurons. By giving them lots of data and adjusting their connections it became possible to train them to distinguish between different kinds of input. They could classify objects or cluster data into groups, and even make predictions about what the next numbers in a sequence might be. These brain-like computer programs enabled computers to check for faults in factory production lines, understand handwriting, or predict prices in the stock market.

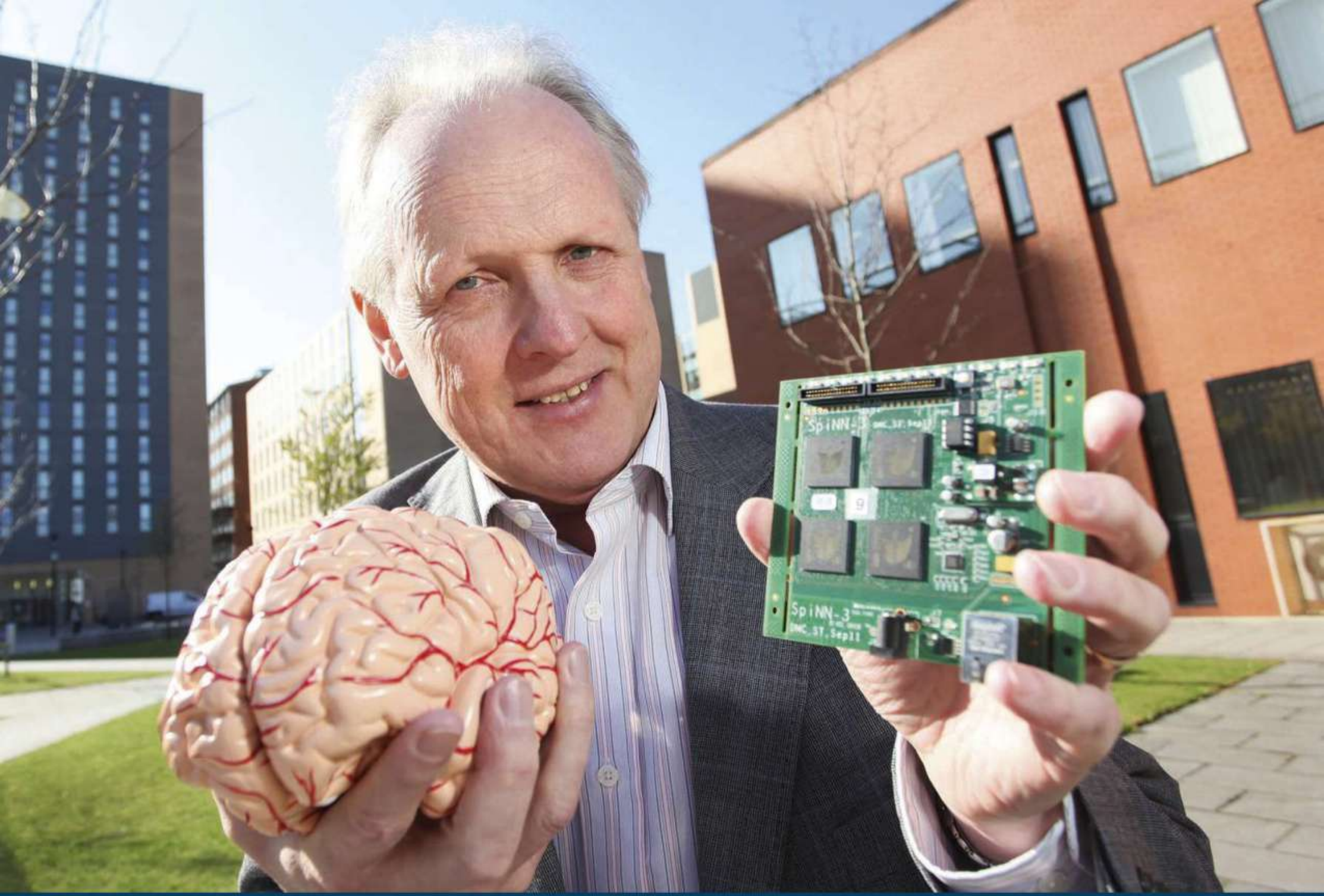
Then, in 2006, there was a breakthrough. Researchers discovered how to organise the networks in 'deep layers' – rows of neurons, connected to more rows, connected to more rows, and so on. When combined with serious computing power and large amounts of data to train the networks, researchers were suddenly able to create artificial brains that could learn far more complex tasks. The deep learning neural networks could now recognise features in images, understand speech, and even learn how to play simple computer games, or board games such as Go.



The success of this approach has caused a flurry of activity in deep learning, and a new crop of AI companies have emerged that all claim to use the approach.

The success of current methods makes Dayan optimistic about the future of AI. "I'd be surprised if we couldn't engineer most aspects of human-level AI (not super-AI, though) within 20 years or so," he predicts. "However, this will not look like a 'faithful' model of the brain."

So how will we make an artificial brain? It is clear that we need faster computers, and new kinds of computers such as SpiNNaker. We also need to understand how real brains work in far greater detail – why neurons are connected in very specific networks, and how those connections enable our thoughts to circulate. It is likely that it will take decades of neuroscience research before we can discover some of



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“I’d be surprised if we couldn’t engineer most aspects of human-level artificial intelligence within 20 years or so”

the secrets hidden inside our skulls. This need for better knowledge has been recognised by the BRAIN Initiative – a massive American research program announced by President Obama in 2013, dedicated to neuroscience, computer modelling, and medicine relating to the brain.

KEEPING IT SIMPLE

There might be faster ways to make artificial brains, perhaps using highly simplified models of neurons such as those used in deep learning, or by getting our most powerful computers learning simultaneously. We’re starting to become better at handling these large neural networks, and we’re discovering that different kinds are good at different kinds of learning.

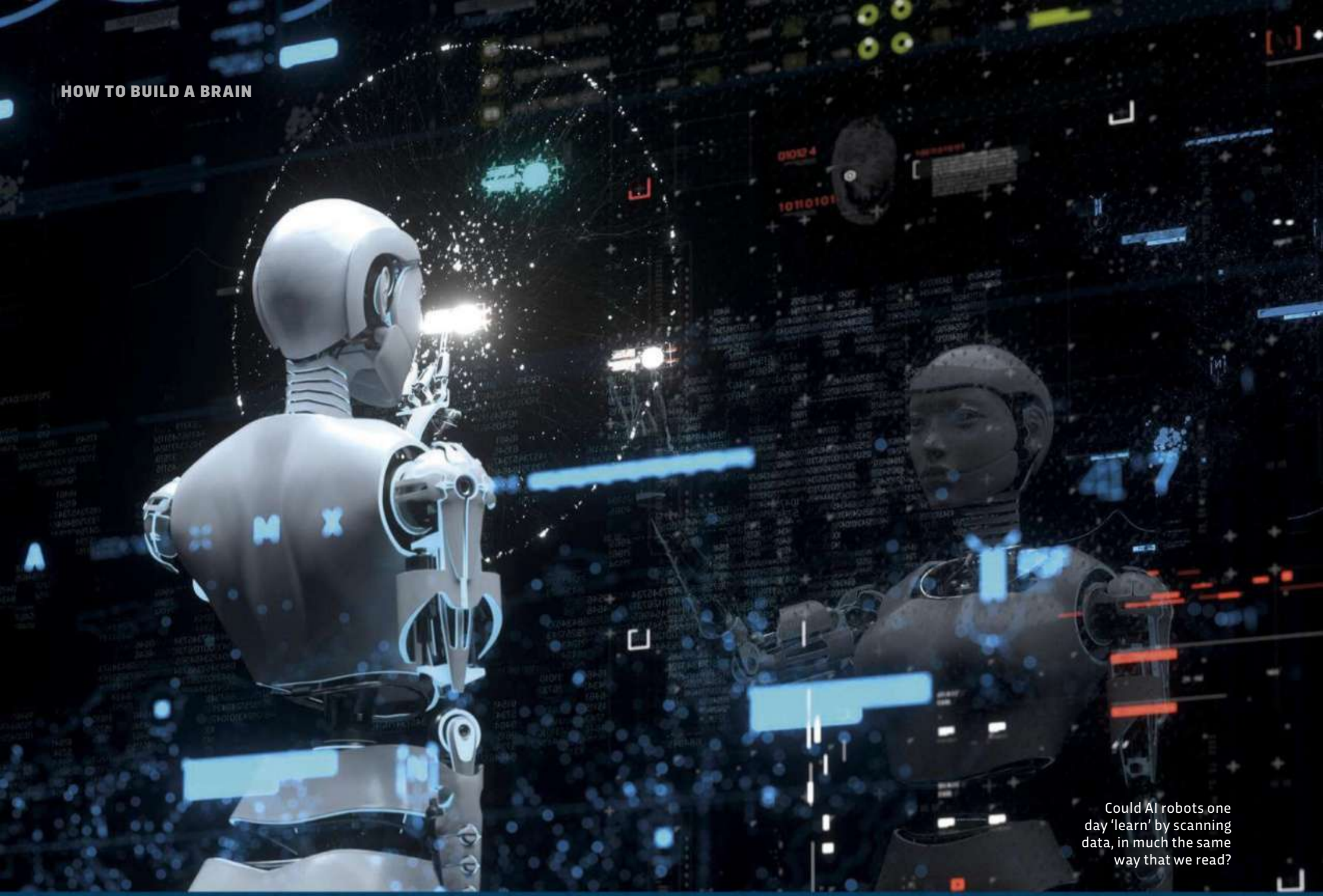
Some researchers try to let the brains design themselves by adding evolution into the mix. After all, our brains evolved because millions of years of challenges helped prune out all the less adaptive, less intelligent brain designs. Using special programs called genetic algorithms, computer scientists are able to evolve neural networks in the same way. There have been some remarkable successes, with ‘virtual creatures’ evolved to swim or run in their virtual worlds, and robot brains evolved to help them navigate the real world. But add evolution into the mix and suddenly you have to multiply the computation power by thousands or millions, so this approach may need another decade or two before our computers can cope.

The alternative approach is to abandon the neurons altogether and try to create software that simply duplicates the functionality ➔

ABOVE LEFT A demonstration of how a Google self-driving car could help the elderly and partially sighted

ABOVE Prof Steve Furber is leading the SpiNNaker project to simulate a human brain

LEFT Software, such as Siri, mimics human intelligence and natural conversation



Could AI robots one day 'learn' by scanning data, in much the same way that we read?

of brains. Memory chips store memories better than brains, so why not use them? It's been a favourite approach for many computer scientists and engineers over the decades, and most practical AIs (such as Apple's Siri and IBM's Watson) are combining several methods in exactly this way.

SEARCHING FOR SOLUTIONS

What is the right approach to make an artificial brain? It probably depends on what you want it to do. But right now the biggest challenges remain unsolved. "They are conceptual rather than technical," says Prof Owen Holland, a pioneer of AI. "We don't really know yet what to do, and so the attention being given to how to do it may be misplaced. Trying to understand and model brains from the neuron up is probably a blind alley given the current state of knowledge, but I'd be very happy to be proved wrong."

And, in several decades, if our artificial brains are starting to reach the complexity of human brains, what then? Will they start to think for themselves as Alan Turing predicted in 1950?

"[Machine consciousness] will happen, and in decades rather than centuries," says Holland. "And instead of thinking about the social consequences of sharing the planet with millions of conscious robots, we should give some thought to the likely consequences of the demonstration that the apparent puzzle and miracle of consciousness is just a natural consequence of a particular arrangement of physical components. How important and precious will our consciousness seem once the mystery is history?" SF

"Machine consciousness will happen, and in decades rather than centuries. We should think about the likely consequences"

by DR PETER BENTLEY *(@peterjbentley)*
Peter is a computer scientist and freelance writer. He is based at University College London.

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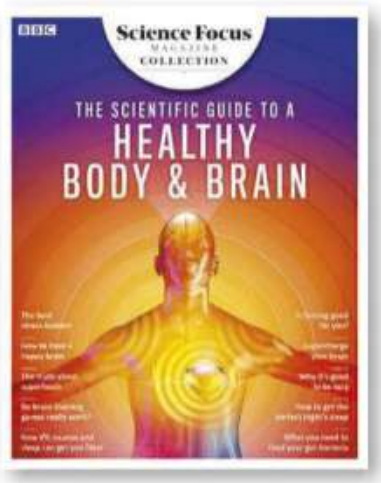

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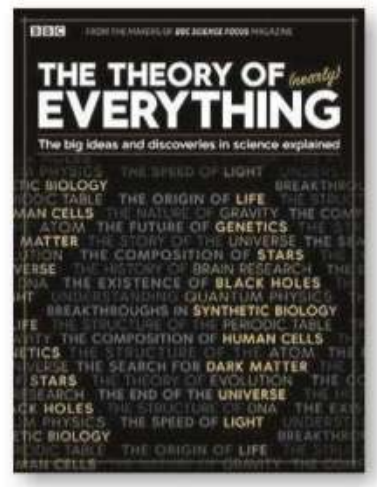

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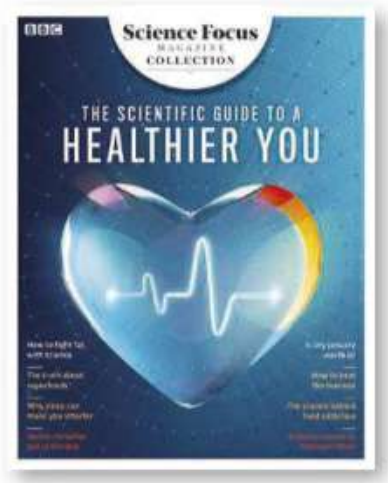

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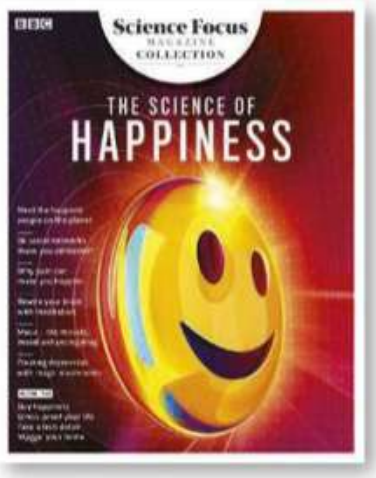

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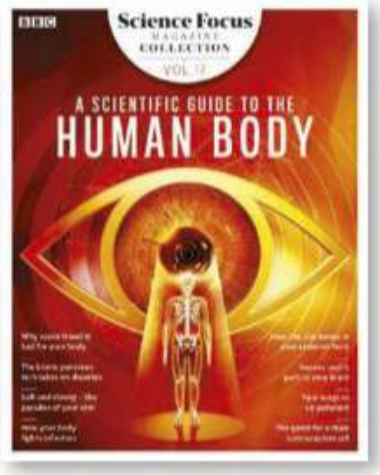

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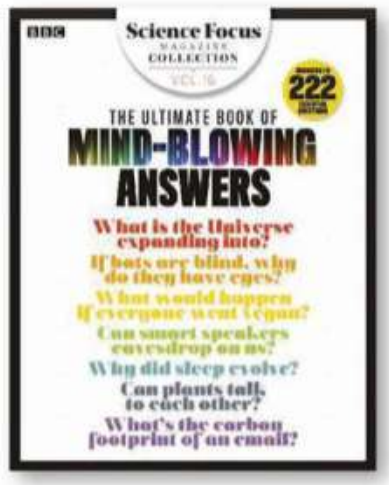

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